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UNITED STATES PATENT APPLICATION

FOR

TREATMENT AND PREVENTION OF OBESITY WITH COX-2 INHIBITORS ALONE OR IN COMBINATION WITH WEIGHT-LOSS AGENTS

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TREATMENT AND PREVENTION OF OBESITY WITH COX-2 INHIBITORS ALONE OR IN COMBINATION WITH WEIGHT-LOSS AGENTS

CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application is related to and claims the priority benefit of U.S. Provisional Patent Application Serial No. 60/451,885 filed March 4, 2003, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to the prevention and treatment of obesity and obesity-related complications, and more particularly to the prevention and treatment obesity and obesity-related complications with a Cox-2 inhibitor alone or in combination with a weight-loss agent.

(2) Description of the Related Art:

[0003] The incidence of obesity has increased dramatically throughout the world, most notably over the last 2 decades. By the year 2000, a total of 38.8 million American adults or 30% of the population met the classification of obesity, defined as having a body mass index score of 30 kg/m^2 or more. *See* Mokdad, A., *et al., JAMA 286*(10):1195-1200 (2001). The deleterious consequences of obesity are considerable. Recent estimates attribute 280,000 deaths a year in the United States to "overnutrition," making it second only to cigarette smoking as a leading cause of death. *See The Merck Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition,* Published by Merck Research Labs, *Sec. 1, Chapter 5, Nutritional Disorders, Obesity* (1999).

[0004] The accumulation of excess fat is a known risk factor for developing many obesity-related complications including hypertension, dyslipidemia, type 2 diabetes, stroke, gallbladder disease, cardiovascular disease, osteoarthritis, hypercholesterolemia, sleep apnea, respiratory problems, cancer, stroke and many other disorders. With regard to this

wide range of health complications, the need to develop new and effective strategies in controlling obesity and obesity-related complications is becoming increasingly important.

[0005] Most attempts to treat obesity to date, except for several types of surgical intervention, have failed to result in a sustained reduction of weight. Moreover, about 90 to 95 percent of persons who lose the weight subsequently regain it. *See* Rosenbaum, *et al., N. Engl. J. Med.* *337*(6):396-407 (1997). Pharmacotherapy treatment principles are limited and have suffered many setbacks in recent years. For example, several obesity drugs have been recalled by the FDA because of incidences of undesirable side effects.

[0006] Currently, the only two FDA-approved anti-obesity drugs are orlistat, a lipase inhibitor, and sibutramine, a serotonin reuptake inhibitor. Orlistat acts by blocking the absorption of fat into the body. An unpleasant side effect with orlistat, however, is the passage of undigested oily fat from the body. Sibutramine is an appetite suppressant that acts by changing the brain levels of serotonin, but in the process, also causes the elevation of blood pressure and an increase in heart rate. Of concern is that both orlistat and sibutramine fail to address the underlying biochemical processes that lead to obesity.

[0007] Other appetite suppressants, such as amphetamine derivatives, are highly addictive and have the potential for abuse. Moreover, different subjects respond differently to weight-loss medications, and some subjects experience more weight loss than others and keep the weight off for longer periods. Thus, current pharmacotherapy treatments are problematic and novel strategies or novel strategies combined with weight-loss agents are needed for the prevention and treatment of obesity and obesity-related disorders.

[0008] In a general sense, obesity results simply from an imbalance in energy intake and utilization. In actuality, however, obesity is a much more complex syndrome stemming from a myriad of both environmental and genetic determinants. Specifically, when the imbalance is a result of

too much energy intake relative to utilization, it ultimately triggers the biochemical process of adipogenesis, which is an increase in size and number of adipocytes (fat cells). Adipogenesis is a two-step developmental process by which an undifferentiated mesenchymal cell differentiates into a pre-adipocyte cell, which then undergoes a secondary differentiation step to become a lipid-filled mature adipocyte.

[0009] The process of pre-adipocyte differentiation is controlled by a cascade of transcription factors, most notably those of the peroxisome proliferator-activated receptor (PPAR) families, which combine to regulate each other and to control the expression of adipocyte-specific genes. One such adipocyte-specific gene, the *obese* (*ob*) gene, was recently identified. *See* Zhang, Y., *et al., Nature 372*:425-432 (1994). The *ob* gene has been found to encode a hormone released by adipose tissue, referred to as leptin, that plays a major role in the regulation of appetite, energy intake and energy expenditure. *See* Halaas, J., *et al., Science 269*(5223):543-6 (1995). Injected leptin has been reported to reduce body weight and food intake in mice through appetite suppression and by increasing the rate of metabolism. *Id.*

[00010] PPARs belong to the nuclear receptor superfamily of ligand-activated transcription factors. Once bound by a ligand, PPARs heterodimerize with 9-cis retinoic acid receptors (RXRs) in the nucleus. These heterodimers bind to specific peroxisome-proliferator response elements (PPRE) in the promoter of target genes, thereby regulating transcription and expression of these genes. Three isoforms of PPARs, alpha, delta (also known as beta or Nuc-1), and gamma, have been identified and differ in their tissue distribution, affinity for particular ligands, and physiological consequences. See *e.g.* Corton, J.C., *et al., Annu. Rev. Pharmacol. Toxicol.* 40:491-518 (2000) and Chawla, A., *et al., Science 294*:1866 - 1870 (2001).

[00011] PPAR-gamma is a nuclear hormone receptor expressed predominantly in adipose tissue. Of particular importance, is that ligand-dependant activation of the PPAR-gamma receptor triggers pre-adipocyte

differentiation. *See* Forman, B., *et al., Cell 83*(5):803-12 (1995). One of the ligands identified as responsible for activation of PPAR-gamma is the naturally occurring prostaglandin, 15-deoxy-delta(12,14)-(15d)-PGJ2 (PGJ2). *See* Kliewer, S., *et al., Cell 1;83(5)*:813-9 (1995).

Cyclooxygenase enzymes (Cox; prostaglandin synthase, EC 1.14.99.1) are responsible for metabolizing arachidonic acid to prostaglandin H_2, which, in turn, serves as a precursor for the biosynthesis of several prostaglandins, including PGJ2. *See e.g.* Hamberg, *et al., Proc. Natl. Acad. Sci. USA 70*:899-903 (1973) and DuBois, R., *et al., Carcinogenesis 19(1)*:49-53 (1998).

[00012] Within the adipogenesis pathway, there are many points at which pre-adipocyte differentiation may be successfully interrupted. For example, expression of the PPAR-gamma receptor itself may be downregulated. Also, synthesis of the PPAR-gamma ligand, PGJ2, may be blocked, thus preventing receptor activation. Inhibiting the synthesis of any other transcription factor or receptor related to adipogenesis initiation should have efficacy against obesity and obesity-related disorders. Moreover, obesity has been implicated on at least one occasion as a disorder that arises as a low-grade systemic inflammatory disease. *See* Das, U., *et al., Nutrition 17*:953-66 (2001). Thus, anti-inflammatory compounds may also slow or inhibit pre-adipocyte differentiation. However, successful treatment of obesity via interruption of the adipogenesis pathway with pharmaceutically acceptable medicaments is currently lacking.

[00013] Historically, physicians have treated inflammation-related disorders with a regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), such as, for example, aspirin and ibuprofen. Undesirably, however, some NSAIDs are known to cause gastrointestinal (GI) bleeding or ulcers in patients undergoing consistent long term regimens of NSAID therapy.

[00014] A reduction of unwanted side effects of common NSAIDs was made possible by the discovery that two cyclooxygenases are involved in

the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway. These enzymes exist in two forms and have been termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). *See* Needleman, P., *et al., J. Rheumatol. 24, Suppl.49*:6-8 (1997) and Fu, J., *et al., J. Biol. Chem. 265(28)*:16737-40 (1990).

[00015] Cox-1 is a constitutive enzyme responsible for the biosynthesis of prostaglandins in the gastric mucosa and in the kidney. Cox-2 is an enzyme that is produced by an inducible gene that is responsible for the biosynthesis of prostaglandins in inflammatory cells. Inflammation causes the induction of Cox-2, leading to the release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity, inflammation, and oedema. *See e.g.* Samad, T. A. *et al., Nature 410*(6827):471-5 (2001). Many common NSAIDs are now known to be inhibitors of both Cox-1 and Cox-2. Accordingly, when administered in sufficiently high levels, these NSAIDs not only alleviate the inflammatory consequences of Cox-2 activity, but also inhibit the beneficial gastric maintenance activities of Cox-1.

[00016] Research into the area of arachidonic acid metabolism has resulted in the discovery of compounds that specifically inhibit the Cox-2 enzyme to a greater extent than the activity of Cox-1. The Cox-2 selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, Cox-2 selective inhibitors have shown great promise for use in therapies -- especially in therapies that require maintenance administration, such as for pain and inflammation control.

[00017] While the effects of Cox-2 inhibitors on inflammation and inflammation-related disorders have been relatively widely recognized, the effects of Cox-2 inhibitors on obesity have not been as widely reported. In fact, it has been reported in at least one instance that Cox-2 inhibitors may actually interfere with successful suppression of pre-adipocyte differention. *See* Yokota, T., *et al., J. Clin. Invest. 109(10)*:1303-10 (2002).

[00018] Despite the recent advances that have been made in understanding the causes for obesity, it remains a largely intractable disorder. It would be useful, therefore, to provide efficacious methods and compositions for the prevention, treatment and amelioration of obesity and obesity-related complications.

SUMMARY OF THE INVENTION

[00019] Briefly, therefore, the present invention is directed to a novel method of preventing and treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor.

[00020] The present invention is also directed to a method of preventing and treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more weight-loss agents.

[00021] The present invention is also directed to a novel therapeutic composition comprising at least one Cox-2 inhibitor and one or more weight-loss agents.

[00022] The present invention is also directed to a novel method of modulating adipogenesis in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with one or more weight-loss agents.

[00023] The present invention is also directed to a pharmaceutical composition comprising a Cox-2 inhibitor, a weight-loss agent, and a pharmaceutically acceptable carrier.

[00024] The present invention is also directed to a novel kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a weight-loss agent.

[00025] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of improved treatment methods and compositions for obesity, the provision of such improved methods and compositions comprising Cox-2 inhibitors alone or in combination with one or more weight-loss agents that are useful for

ameliorating, treating and preventing obesity and obesity-related complications.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00026] In accordance with the present invention, it has been discovered that obesity and obesity-related complications may be treated, prevented, and ameliorated in a subject by administering to the subject a Cox-2 inhibitor alone or in combination with one or more weight-loss agents.

[00027] For purposes of the present invention, the novel monotherapy or combination therapy comprising at least one Cox-2 inhibitor alone or in combination with at least one weight-loss agent is also useful for the purpose of preventing and treating obesity and obesity-related complications in a subject that is in need of such prevention and treatment.

[00028] Thus, the monotherapy or combination therapy of the present invention would be useful, for example, to cause weight loss in an overweight or obese subject or in any subject who desires to lose weight, to reduce the death rate or the number of hospitalizations, or to prevent or retard, in subjects, the development of complications associated with being overweight or obese, such as, for example, diabetes, cardiovascular diseases, hypertension, hypercholesteremia, and stroke, which eventually arise from being chronically overweight or obese.

[00029] The administration of a Cox-2 inhibitor for the prevention and treatment of obesity and obesity-related complications is unexpectedly an effective treatment therapy. Such administration is effective for improving the symptoms of obesity and obesity-related complications without the disadvantages of current treatments.

[00030] Furthermore, the administration of a Cox-2 inhibitor in combination with a weight-loss agent for the prevention or treatment of obesity or obesity-related complications is an effective treatment for obesity or obesity-related complications, and in preferred embodiments, is superior to the use of either agent alone. For example, the combination therapy is effective for lowering the dosages of weight-loss agents that are normally prescribed as a monotherapy. The administration of lower

dosages of weight-loss treatment agents provides a reduction in side effects corresponding to such agents. Moreover, in preferred embodiments, the combination therapy demonstrates a synergistic efficacy for treating and preventing obesity and obesity-related complications that is greater than what would be expected from simply combining the two therapies.

[00031] As used herein, the term "obesity" is defined as having a high amount of body fat or adipose tissue in relation to lean body mass. Obesity may arise in a subject via several determinants including environmental, physiological, and genetic determinants. *See The Merck Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition,* Published by Merck Research Labs, *Sec. 1, Chapter 5, Nutritional Disorders, Obesity* (1999). For the present invention, however, the term "obesity" is meant to include any fat or weight in a subject who desires to lose such weight or fat. Thus, reference to the "treatment or prevention of obesity" encompasses any subject who desires to reduce their body weight or reduce adipose (fat) tissue mass.

[00032] Accordingly, the methods and compositions of the present invention encompass the treatment or prevention of obesity by causing the loss of weight (weight-loss) in a subject who desires or requires weight-loss. The amount of body fat (or adiposity) includes concern for both the distribution of fat throughout the body and the size of the adipose tissue deposits.

[00033] For example, professional athletes may, on occasion, need to lose additional weight even though their weights would have been considered ideal or normal before following the methods of the present invention or taking the compositions taught herein. Therefore, the present invention encompasses a subject who simply desires to lose weight and is not necessarily suffering from obesity or being overweight or suffering from a weight-related disorder. The present invention's methods and compositions encompass such weight-loss in those individuals through the "treatment or prevention of obesity."

[00034] As used herein, the term "overweight" refers to increased body weight in relation to height, when compared to a desirable weight. However, overweight may or may not be due to increases in body fat. It may also be due to an increase in lean muscle. For example, professional athletes may be very lean and muscular, with very little body fat, yet they may weigh more than others of the same height. While they may qualify as "overweight" due to their large muscle mass, they are not necessarily "overly fat." However, the present invention encompasses methods and compositions that provide weight loss to a subject that desires weight loss regardless of whether they are overly fat, overweight, or obese.

[00035] As used herein, the term "obesity-related complication" refers to any condition where the accumulation of excess fat is a risk factor for developing health complications. Over time, weight loss in obese individuals may reduce a number of health risks. Studies looking at the effects of weight-loss medication treatment on obesity-related health risks have found that some agents lower blood pressure, blood cholesterol, and triglycerides (fats) and decrease insulin resistance (the body's inability to use blood sugar) via a reduction in weight.

[00036] For purposes of the present invention, obesity-related complications include, but are not limited to, hypertension, dyslipidemia, type 2 diabetes, stroke, gallbladder disease, cardiovascular disease, osteoarthritis, rheumatoid arthritis, hypercholesterolemia, stable angina, unstable angina, artherosclerosis, sleep apnea, respiratory problems, cancer, stroke and many other disorders. Thus, the reduction of excess fat by the methods and compositions of the present invention also helps to prevent or to treat any health complication arising from the condition of having the excess fat.

[00037] Accordingly, the methods and compositions of the present invention treat or prevent obesity-related health complications. In animals and model organisms, diet induced weight loss or low caloric diets have provided evidence for increased longevity of the animals. This may be due to either the absence of disease causing life shortening, or actual

extended lifespan. Therefore, the treatments described herein provide a healthier, more productive and longer lifespan for both animals and humans.

[00038] The compositions and methods of the present invention also encompass the post surgical maintenance of weight loss, from liposuction or more direct surgical resection of adipose in that adipose differentiation is inhibited and thus, the accumulation of new fat/adipose mass will be reduced allowing for reduced numbers of repeat procedures and complications arising therefrom.

[00039] In the present invention, a Cox-2 inhibitor alone or in combination with a weight-loss agent is administered to a subject according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor alone or in combination with the weight-loss agent depends upon the needs of the subject being treated, the type of treatment, the efficacy of the compound and the degree of obesity severity in the subject.

[00040] It is preferred that the amount of a Cox-2 inhibitor that is administered to a subject comprises an effective amount of a Cox-2 inhibitor. It is further preferred that the amount of a Cox-2 inhibitor and the amount of a weight-loss agent together comprise an effective amount of the combination of the two treatment agents. Still further preferred is that the amount of the monotherapy with the Cox-2 inhibitor comprises a therapeutically amount of the Cox-2 inhibitor. Further preferred is that the amount of the co-therapy with the Cox-2 inhibitor and weight-loss agent comprise a therapeutically effective amount of the co-therapy.

[00041] As used herein, an "effective amount" means the dose or amount to be administered to a subject and the frequency of administration to the subject, which is readily determined by one having ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances.

[00042] In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to,

the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[00043] As used herein, the terms "therapeutically effective" are intended to qualify the amount of an agent for use in therapy which will achieve the goal of preventing, or improvement in the severity of, the disorder being treated, while avoiding adverse side effects typically associated with alternative therapies. An obesity symptom or an obesity-related complication symptom is considered ameliorated or improved if any benefit is achieved, no matter how slight. For example, any reduction in the weight of a subject would be considered an ameliorated symptom. Likewise, any alteration of the normal process of adipogenesis would be considered amelioration of an obesity symptom. Furthermore, any reduction in symptom severity of an obesity-related complication is considered an ameliorated symptom. An obesity-related complication, such as hypertension, is considered ameliorated, if after administration of the compositions and methods of the present invention, a reduction in blood pressure is found.

[00044] As used herein, the terms "prophylactically effective" refer to an amount of a Cox-2 inhibitor alone or in combination with a weight-loss agent that causes a decrease in the frequency of incidence of obesity or an obesity-related complication. The term "prophylactic" refers to the prevention of obesity or an obesity-related complication, whereas the term "therapeutic" refers to the effective treatment of an existing disorder such as obesity or an obesity-related complication.

[00045] As used herein, the phrases "combination therapy", "co-administration", "co-administering", "administration with", "administering", "combination", or "co-therapy", when referring to use of a Cox-2 inhibitor in combination with a weight-loss agent, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well

to embrace co-administration of these agents in a substantially simultaneous manner. Thus, the Cox-2 inhibitor and weight-loss agent may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[00046] Sequential administration of such treatments encompasses both relatively short and relatively long periods between the administration of each of the two drugs of the present method. However, for purposes of the present invention, the second drug is administered while the first drug is still having an efficacious effect on the subject. Thus, the present invention takes advantage of the fact that the simultaneous presence of the combination of a Cox-2 inhibitor and a weight-loss agent in a subject has a greater efficacy than the administration of either agent alone.

[00047] Preferably, the second of the two drugs is to be given to the subject within the therapeutic response time of the first drug to be administered. For example, the present invention encompasses administration of a Cox-2 inhibitor to the subject and the later administration of a weight-loss agent, as long as the weight-loss agent is administered to the subject while the Cox-2 inhibitor is still present in the subject at a level, which in combination with the level of the weight-loss agent is therapeutically effective, and vice versa.

[00048] As used herein, the terms "therapeutic response time" mean the duration of time that a compound is present within a subject's body at therapeutic concentrations.

[00049] As used herein, the term "monotherapy" is intended to embrace administration of a Cox-2 inhibitor to a subject suffering from an obesity or obesity-related complication as a single therapeutic treatment without an additional therapeutic treatment comprising a weight-loss agent. However, the Cox-2 inhibitor may still be administered in multiple dosage forms. Thus, the Cox-2 inhibitor may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate

therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[00050] As used herein, the terms "treating" or "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of obesity associated with, but not limited to, any of the diseases or disorders described herein.

[00051] The present invention is also directed to a novel method of treating or preventing obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more weight-loss agents.

[00052] Without being bound by this or any other theory, it is believed that a therapy comprising a Cox-2 inhibitor is efficacious for impairing the process of adipogenesis, thus preventing or treating obesity and thereby an obesity-related complication. Obesity is a known factor or contributor to generalized inflammatory states and proinflammatory cytokines are produced that affect general health and may predispose toward or exacerbate other causes of inflammation in the body. As Cox-2 inhibitors are effective anti-inflammatory agents, the administration of these agents have beneficial effects in the obese population directly from their anti-inflammatory properties.

[00053] Moreover, in preferred embodiments, the combination of a Cox-2 inhibitor and a weight-loss agent provide synergistic effects, which reduces the symptoms associated with obesity and obesity-related complications to a greater extent than either one alone. The term "synergistic" refers to the combination of a Cox-2 inhibitor and a weight-loss agent as a combined therapy having an efficacy for the prevention and treatment of obesity that is greater than what would be expected on the basis of their individual effects.

[00054] The synergistic effects of preferred embodiments of the present invention's combination therapy encompass additional unexpected

advantages for the treatment and prevention of obesity. Such additional advantages include, but are not limited to, lowering the required dose of weight-loss agents, reducing the side-effects of weight-loss agents, and rendering those agents more tolerable to subjects in need of obesity therapy.

[00055] Also, the monotherapy and combination therapy of the present invention provide for the treatment of obesity-related complications, which arise indirectly from being obese, by treating the underlying obesity itself. For example, if an obese subject is suffering from obesity-related complications, such as diabetes and hypertension, the treatment of the underlying obesity by the methods and compositions of the present invention will likewise improve the symptoms of the associated complications.

[00056] In one embodiment, the present invention provides a method of preventing obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with a weight-loss agent.

[00057] As used herein, the terms "to prevent", "preventing", or "prevention" refer to any reduction, no matter how slight, of a subject's predisposition or risk for developing obesity and/or an obesity-related complication. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing obesity and/or an obesity-related complication.

[00058] As used herein, a subject that is "predisposed to developing obesity and/or an obesity-related complication" or "at risk for developing obesity and/or an obesity-related complication," both of which are used interchangeably herein, includes any subject with an increased chance for developing obesity and/or an obesity-related complication. The subject may be at risk due to genetic predisposition, diet, sedentary lifestyle, age, exposure to obesity-causing agents, and the like. The subject may be at risk due to physiological factors such as anatomical and biochemical abnormalities and certain hormonal diseases or disorders. For example,

the subject may be at risk due to such physiological factors as excessively high levels of adipogenesis. The subject may also be at risk for re-developing obesity during a relapse of such a disorder.

[00059] In one embodiment, the present invention provides a method of treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with a weight-loss agent.

[00060] As used herein, the terms "treating", “treatment”, “treated”, or "to treat," mean to alleviate obesity symptoms, eliminate the causation either on a temporary or permanent basis, or to alter or slow the appearance of obesity symptoms or symptom worsening. The term "treatment" includes alleviation or elimination of the causation of obesity, including any of the obesity-related complications described herein.

[00061] A component of the present invention is a Cox-2 inhibitor.

[00062] Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid may inhibit enzyme activity through a variety of mechanisms. By way of example, the Cox-2 inhibitors used in the methods described herein may block the enzyme activity directly by binding at the substrate site of the enzyme. In preferred embodiments, the use of a Cox-2 selective inhibitor is highly advantageous in that it minimizes the gastric side effects that can occur with non-selective non-steroidal anti-inflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

[00063] The terms “cyclooxygenase-2 inhibitor”, or “Cox-2 inhibitor”, which can be used interchangeably herein, embrace compounds, which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include pharmaceutically acceptable salts of those compounds. Thus, for purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to an equal, greater, or lesser degree than the Cox-1 enzyme.

[00064] In one embodiment of the present invention, it is preferred that the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug (NSAID). Therefore, preferred materials that can serve as the Cox-2 inhibitor of the present invention include non-steroidal anti-inflammatory drug compounds, a pharmaceutically acceptable salt thereof, or a pure (-) or (+) optical isomeric form thereof.

[00065] Examples of NSAID compounds that are useful in the present invention include acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid, carprofen, choline magnesium trisalicylate, clidanac, clopinac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenec, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, feprazone, flufenamic acid, fluprofen, ibufenac, ibuprofen, indometacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, miroprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxipinac, oxyphenbutazone, phenylbutazone, podophyllotoxin derivatives, proglumetacin, piprofen, pirprofen, prapoprofen, salicylic acid, salicylate, sudoxicam, suprofen, sulindac, tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, zidometacin, zomepirac, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

[00066] Further preferred NSAID compounds include ibuprofen, naproxen, sulindac, ketoprofen, fenoprofen, tiaprofenic acid, suprofen, etodolac, carprofen, ketrolac, piprofen, indoprofen, salicylic acid, and flurbiprofen.

[00067] In a preferred embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor. The term "Cox-2 selective inhibitor" embraces compounds, which selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme, and also include pharmaceutically acceptable salts and prodrugs of those compounds.

[00068] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

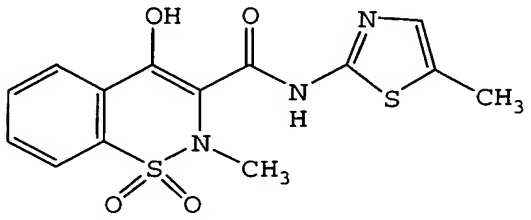
[00069] As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00070] Preferred Cox-2 selective inhibitors have a Cox-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

[00071] Also included within the scope of the present invention are compounds that act as prodrugs of Cox-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is sodium parecoxib. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

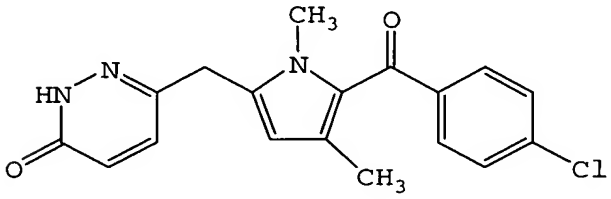
[00072] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS

registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

[00073] In another embodiment of the invention the Cox-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[00074] The meaning of any substituent at any one occurrence in Formula I, or any other general chemical formula herein, is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

[00075] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The number of carbon atoms can also be expressed as "C_1-C_5", for example. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like. The term

"alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like. The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[00076] The term "oxo" means a single double-bonded oxygen.

[00077] The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2 -) radical.

[00078] The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. Likewise, the term “halo”, when it is appended to alkenyl, alkynyl, alkoxy,

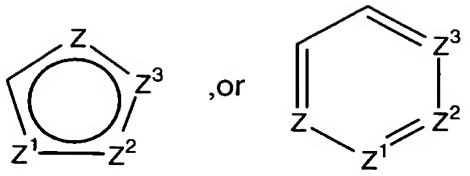
aryl, cycloalkyl, heteroalkyl, heteroaryl, and the like, includes radicals having mono-, di-, or tri-, halo substitution on one or more of the atoms of the radical.

[00079] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

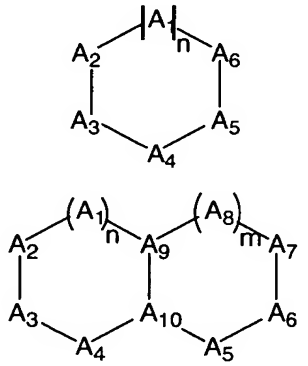
[00080] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and diaikoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. Terms such as "alkoxy(halo)alkyl", indicate a molecule having a terminal alkoxy that is bound to an alkyl, which is bonded to the parent molecule, while the alkyl also has a substituent halo group in a non-terminal location. In other words, both the alkoxy and the halo group are substituents of the alkyl chain.

[00081] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl.

[00082] The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The terms aryl or heteroaryl, as appropriate, include the following structures:



where:

when n=1, m=1 and A_1-A_8 are each CR^x or N, A_9 and A_{10} are carbon;

when n=0, or 1, and m=0, or 1, one of A_2-A_4 and/or A_5-A_7 is optionally S, O, or NR^x, and other ring members are CR^x or N, with the

proviso that oxygen cannot be adjacent to sulfur in a ring. A_9 and A_{10} are carbon;

when n is greater than or equal to 0, and m is greater than or equal to 0, 1 or more sets of 2 or more adjacent atoms A_1-A_{10} are sp3 O, S, NR^x, CR^xR^y, or C=(O or S), with the proviso that oxygen and sulfur cannot be adjacent. The remaining A_1-A_8 are CR^x or N, and A_9 and A_{10} are carbon;

when n is greater than or equal to 0, and m greater than or equal to 0, atoms separated by 2 atoms (*i.e.*, A_1 and A_4) are Sp3 O, S, NR^x, CR^xR^y, and remaining A_1-A_8 are independently CR^x or N, and A_9 and A_{10} are carbon.

[00083] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2$-NH_2), which may also be termed an "aminosulfonyl". The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical.

[00084] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2$-H. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes – (C=O) –. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3 – (CO) –. The term "alkylcarbonylalkyl" denotes an alkyl radical

substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3$-C-O–C=O) – and – (O=)C– OCH_3. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(CH_3)_3$C-OC(=O)-$(CH_2)_2$ – and – $(CH_2)_2$ (–O)$COCH_3$. The terms "amido", or "carbamyl", when used alone or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkylradical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkylradicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an –C(–NH)–NH_2 radical. The term "cyanoamidin" denotes an –C(–N–CN) –NH_2 radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl.

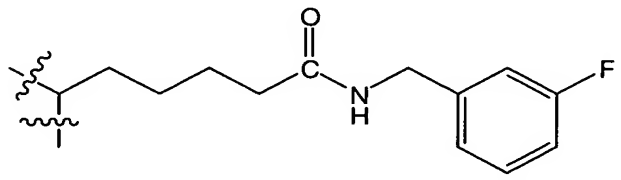
[00085] The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[00086] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3 –S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(–O) – atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00087] The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino (CH_3-C(=O) –NH–).

[00088] In the naming of substituent groups for general chemical structures, the naming of the chemical components of the group is typically from the terminal group-toward the parent compound unless otherwise noted, as discussed below. In other words, the outermost chemical structure is named first, followed by the next structure in line, followed by the next, etc. until the structure that is connected to the parent structure is named. For example, a substituent group having a structure such as:



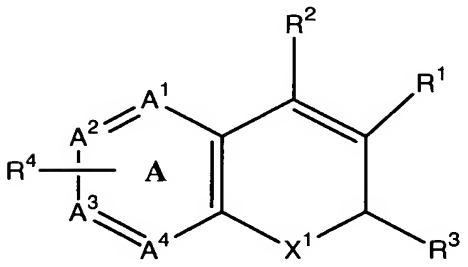
may be referred to generally as a "haloarylalkylaminocarboxylalkyl". An example of one such group would be fluorophenylmethylcarbamylpentyl.

The bonds having wavy lines through them represent the parent structure to which the alkyl is attached.

[00089] Substituent groups may also be named by reference to one or more "R" groups. The structure shown above would be included in a description, such as, "-C_1-C_6-alkyl-COR^u, where R^u is defined to include -NH-C_1-C_4-alkylaryl-R^y, and where R^y is defined to include halo. In this scheme, atoms having an "R" group are shown with the "R" group being the terminal group (*i.e.*, furthest from the parent). In a term such as "$C(R^x)_2$", it should be understood that the two R^x groups can be the same, or they can be different if R^x is defined as having more than one possible identity.

[00090] In one embodiment of the present invention, the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses substituted benzopyrans or substituted benzopyran analogs, as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00091] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 –alkyl and C_2 –C_6 –alkenyl;

wherein R^3 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

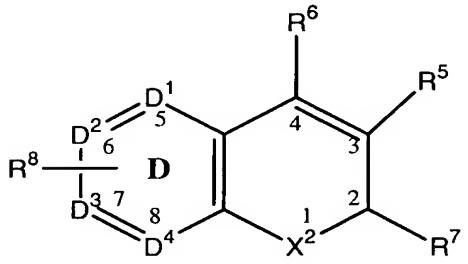
wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-$_1$ –C_3 –hydroxyalkyl, C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_1 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt thereof.

[00092] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes compounds having the structure of formula **II**:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

or wherein $CR^c R^b$ form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 –C_6 –alkynyl and C_2 –C_6 –alkenyl;

wherein R^7 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –

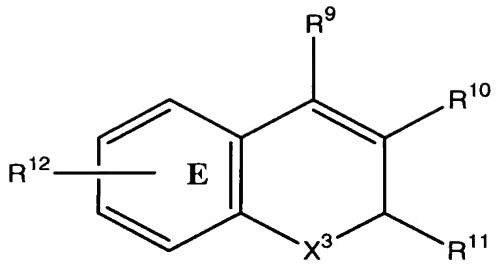
alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, —$O(CF_2)_2$ O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-C_1 –C_3 –hydroxyalkyl), C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_6 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt thereof.

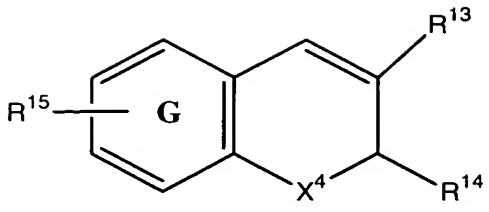
[00093] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula **III**:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;
wherein R^a is alkyl;
wherein R^9 is selected from the group consisting of H and aryl;
wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;
wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and
wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and
including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00094] A related class of compounds useful as Cox-2 selective inhibitors in the present invention is described by Formulas **IV** and **V** below:



IV

wherein X^4 is selected from O or S or NR^a ;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

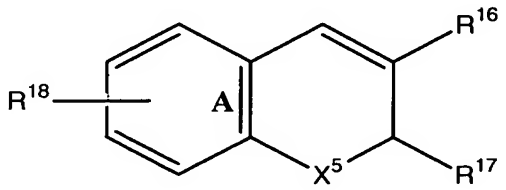
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00095] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00096] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing

heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00097] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00098] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-

phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;
or an isomer or pharmaceutically acceptable salt thereof.

[00099] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

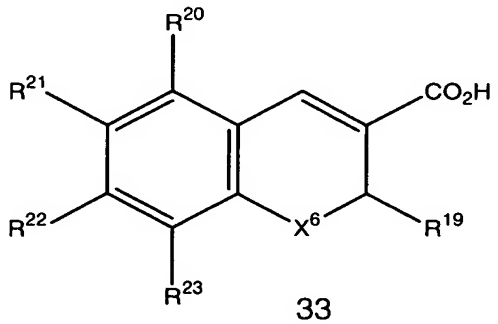
X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;
or an isomer or prodrug thereof.

[000100] The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

[000101] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

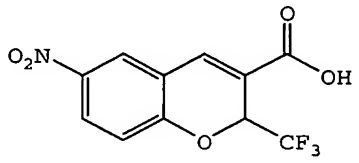
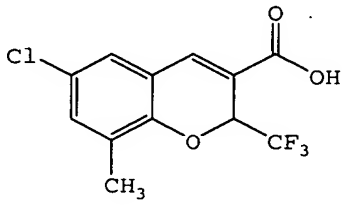
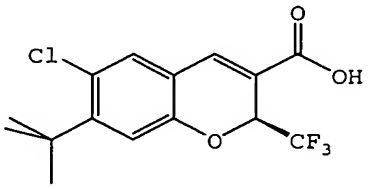
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

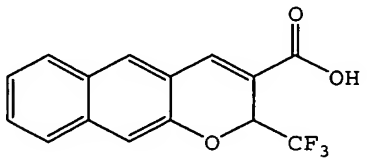
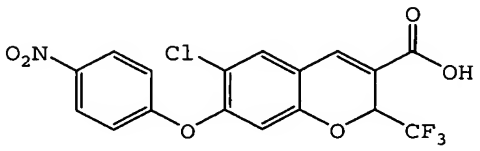
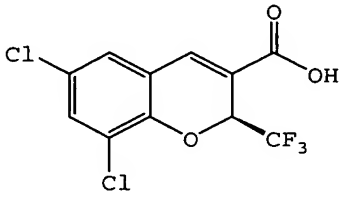
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

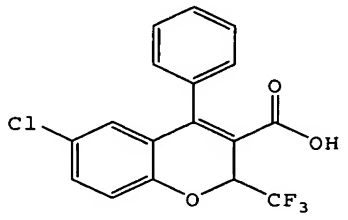
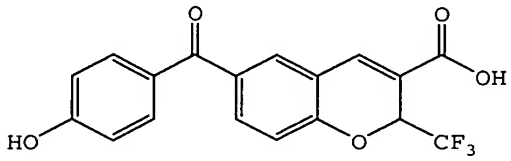
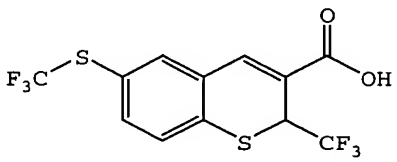
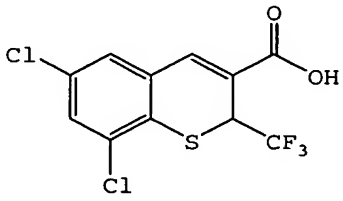
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

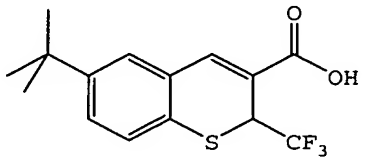
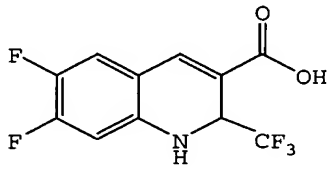
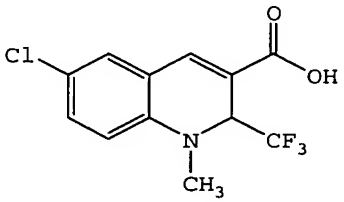
or an isomer or prodrug thereof.

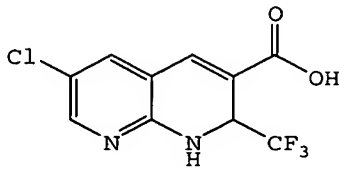
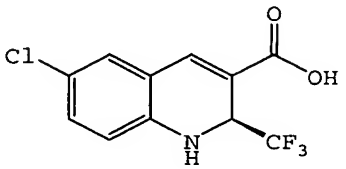
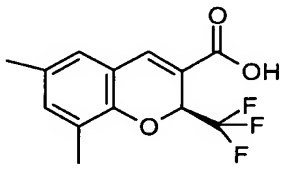
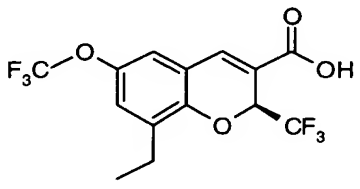
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

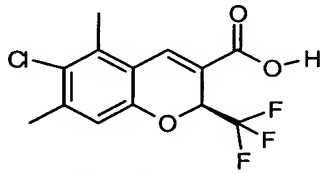
Compound Number	**Structural Formula**
B-3	 6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-18	 (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-19	 (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

Compound Number	Structural Formula
B-20	 (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

[000102] In preferred embodiments, the chromene Cox-2 inhibitor is comprises at least one compound selected from the group consisting of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

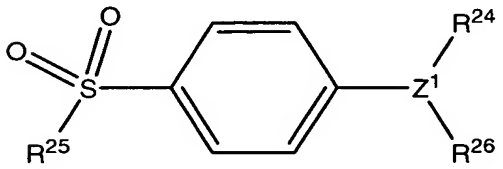
6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.
6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-(difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6,8-dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
5,6-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
2,6-bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,7,8-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6-bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6-chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid, and mixtures thereof.

[000103] In further preferred embodiments, the chromene Cox-2 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.

[000104] In a preferred embodiment of the invention, the Cox-2 inhibitor can be selected from the class of tricyclic Cox-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a

substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

or a prodrug thereof.

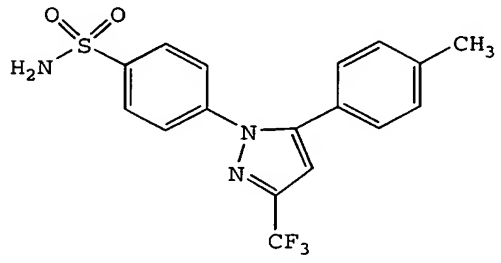
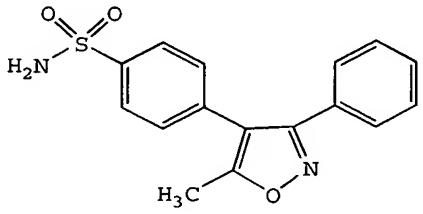
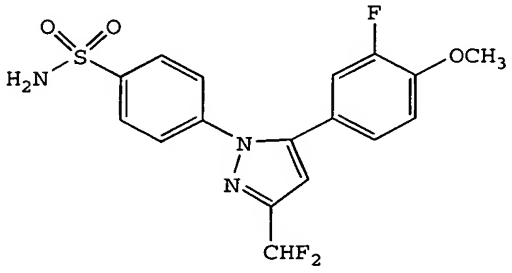
[000105] In a preferred embodiment of the invention, the tricyclic Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

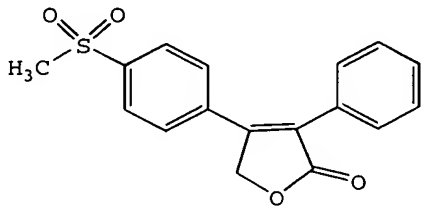
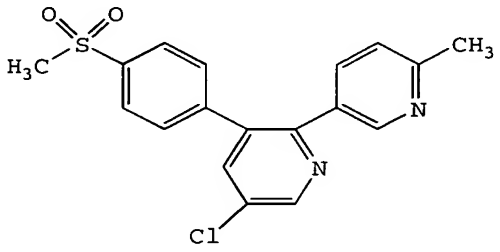
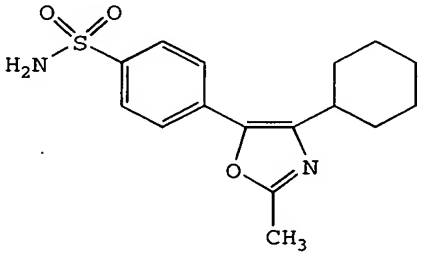
[000106] In a further preferred embodiment of the invention, the Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

[000107] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib

(CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

Table 2. Examples of Tricyclic Cox-2 Selective Inhibitors

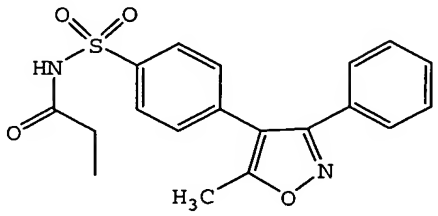
Compound Number	**Structural Formula**
B-21	
B-22	
B-23	

Compound Number	Structural Formula
B-24	
B-25	
B-26	

[000108] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

[000109] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor

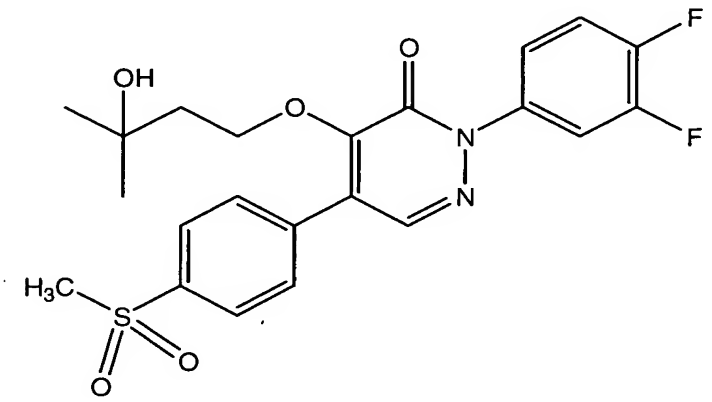
valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.



B-27

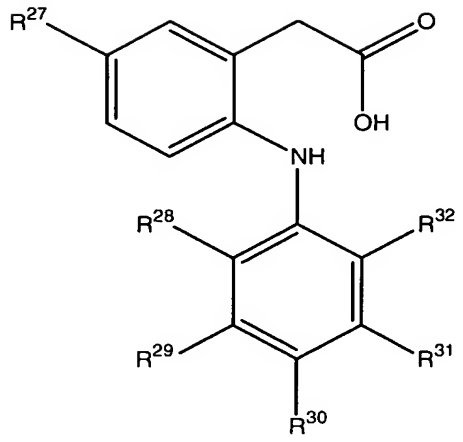
[000110] A preferred form of parecoxib is sodium parecoxib.

[000111] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication Number WO 00/24719.



B-28

[000112] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[000113] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[000114] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[000115] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as Cox-189 (also termed lumiracoxib; CAS Reg. No. 220991-20-8), having the structure shown in formula **VIII**,

wherein:

R^{27} is methyl;

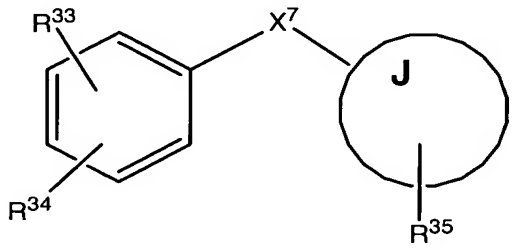
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[000116] Compounds having a structure similar to that shown in formula **VIII**, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099, 6,291,523, and 5,958,978.

[000117] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X^7 is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), or

X^7 is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); or

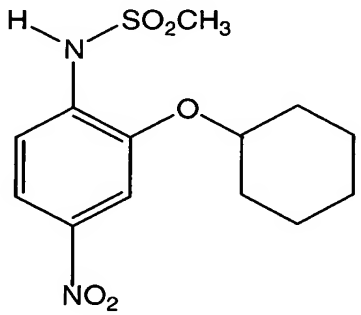
X^7 is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); or

X^7 is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); or

X^7 is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); or

X^7 is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

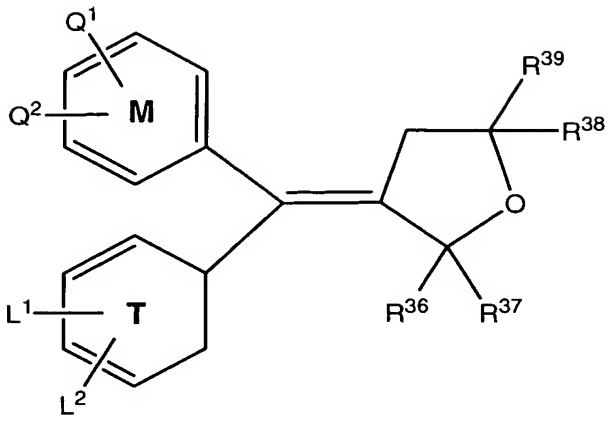
[000118] The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4):*406 – 412 (1999).



B-29

[000119] An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[000120] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is an $—S(O)_n—R$ group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an $–SO_2NH_2$ group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom; or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

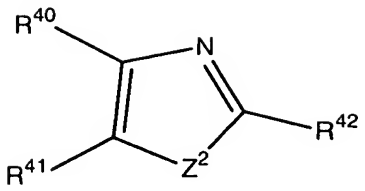
[000121] Particular diarylmethylidenefuran derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[000122] Other Cox-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[000123] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[000124] Conjugated linoleic, as described in U.S. Patent No. 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[000125] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

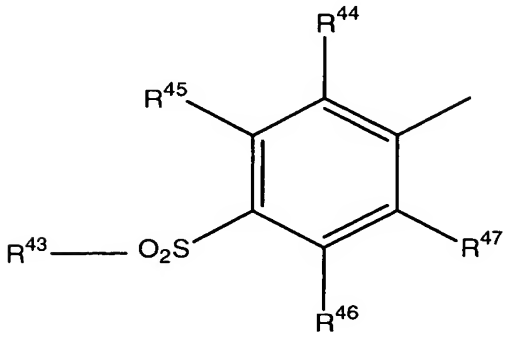


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



wherein:

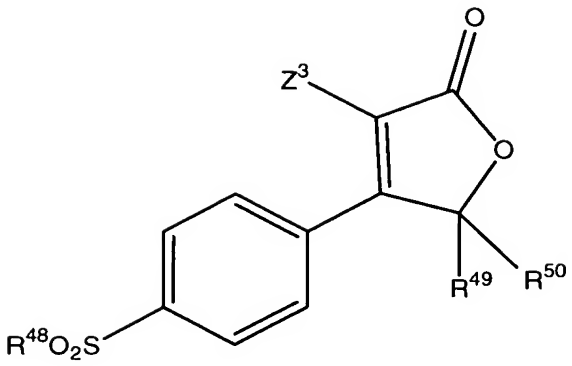
R^{43} is lower alkyl, amino or lower alkylamino; and

R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino, provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl,

and a pharmaceutically acceptable salt thereof.

[000126] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of linear or branched C_1 –C_6 alkyl, linear or branched C_1 –C_6 alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of hydrogen, halo, C_1 –C_3 alkoxy, CN, C_1 –C_3 fluoroalkyl C_1 –C_3 alkyl, and –CO_2 H;

R^{48} is selected from the group consisting of NH_2 and CH_3,

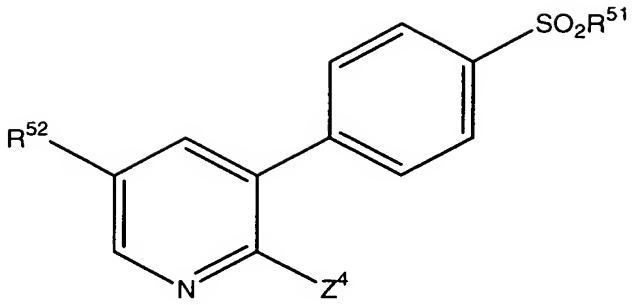
R^{49} is selected from the group consisting of C_1 –C_6 alkyl unsubstituted or substituted with C_3 –C_6 cycloalkyl, and C_3 –C_6 cycloalkyl;

R^{50} is selected from the group consisting of:

C_1 –C_6 alkyl unsubstituted or substituted with one, two or three fluoro atoms, and C_3 –C_6 cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[000127] Pyridines that are described in U.S. Patent Nos. 6,596,736, 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and can serve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

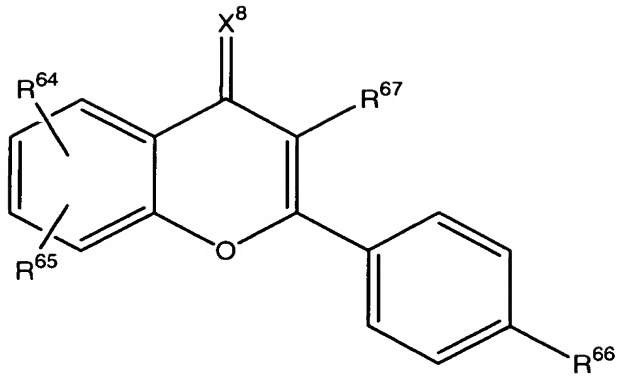
Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are chosen from the group consisting of hydrogen, halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, $–CO_2R^{53}$, hydroxyl, $–C(R^{54})(R^{55})—OH$, – C_1 –C_6 alkyl-$CO_2—R^{56}$, C_1 –C_6 fluoroalkoxy;

R^{52} is chosen from the group consisting of: halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, $—CO_2R^{57}$, hydroxyl, $—C(R^{58})(R^{59})—OH$, — C_1 –C_6 alkyl-$CO_2—R^{60}$, C_1 –C_6 fluoroalkoxy, NO_2, $NR^{61}R^{62}$, and $NHCOR^{63}$;

R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, and R^{63}, are each independently chosen from the group consisting of hydrogen andC_1 –C_6 alkyl;

or R^{54} and R^{55}, R^{58} and R^{59}, or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[000128] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

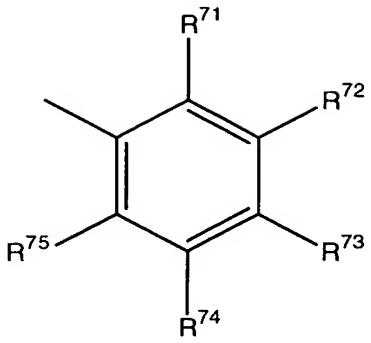
wherein:

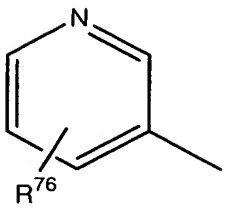
X^8 is an oxygen atom or a sulfur atom;

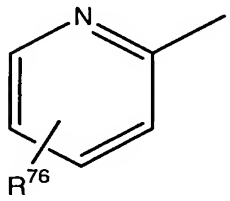
R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrile group, or a carboxyl group;

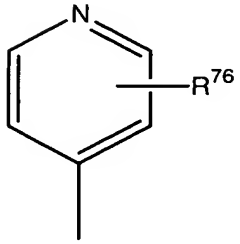
R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is a hydrogen atom, a C_1 –C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 –C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 –C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:









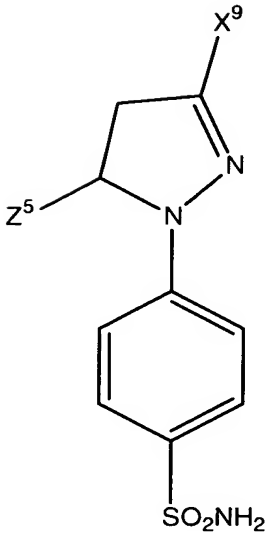
wherein:

R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

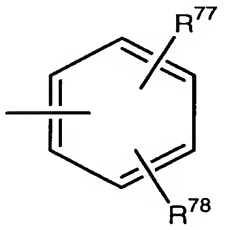
[000129] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 –C_6 trihalomethyl, preferably trifluoromethyl; C_1 –C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



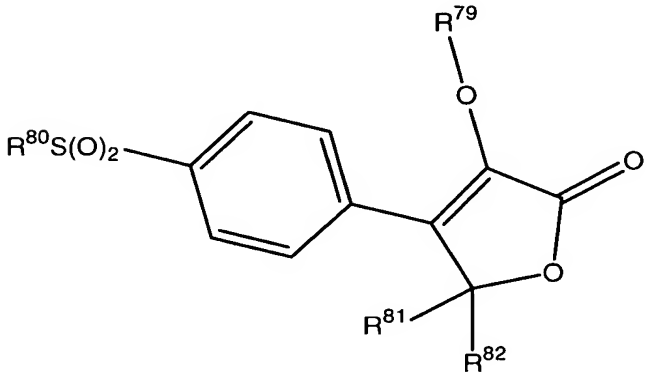
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 –C_6 alkyl, preferably C_1 –C_3 alkyl; C_1 –C_6 alkoxy, preferably C_1 – C_3 alkoxy; carboxy; C_1 –C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[000130] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

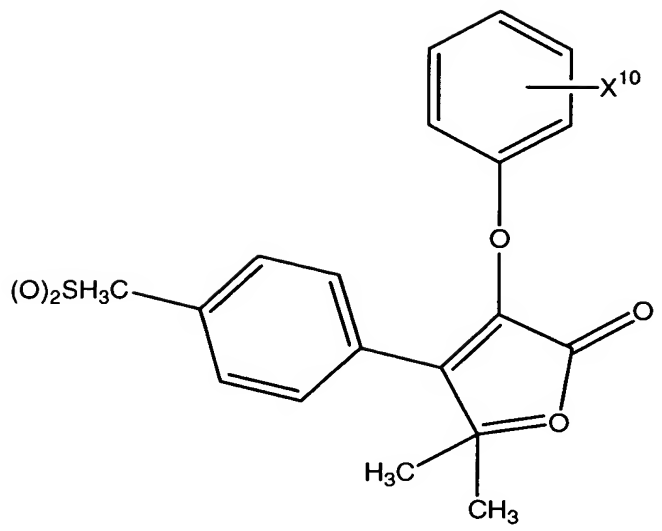
R^{79} is a mono-, di-, or tri-substituted C_1 –C_{12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_3 –C_{12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_5 –C_{12} cycloalkynyl, wherein the substituents are chosen from the group consisting of halo selected from F, Cl, Br, and I, OH, CF_3, C_3 – C_6 cycloalkyl, =O,dioxolane, CN;

R^{80} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

R^{81} and R^{82} are independently chosen from the group consisting of hydrogen and C_1 –C_{10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

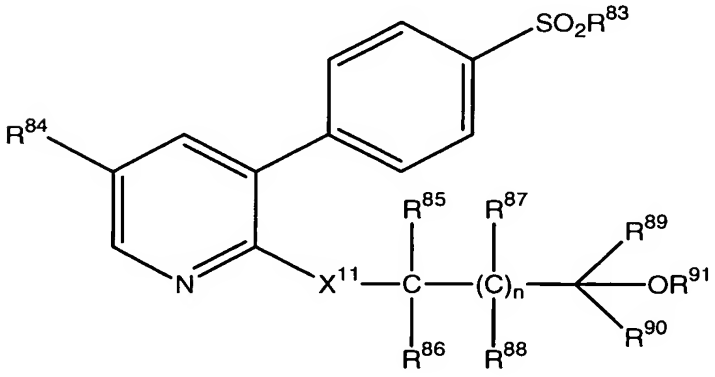
[000131] Formula **XVIII** is:



XVIII

wherein X^{10} is fluoro or chloro.

[000132] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

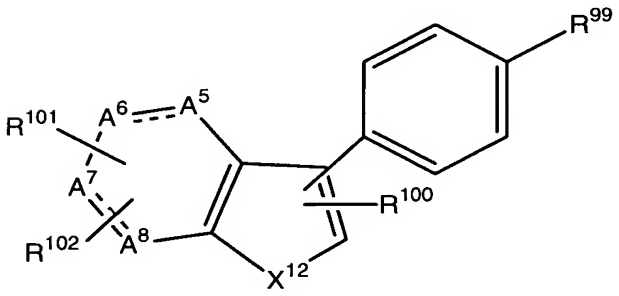
wherein:

X^{11} is selected from the group consisting of O, S, and a bond;

n is 0 or 1;

R^{83} is selected from the group consisting of CH_3, NH_2, and $NHC(O)CF_3$;
R^{84} is chosen from the group consisting of halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2 R^{92}, hydroxyl, —$C(R^{93})(R^{94})$—OH, —C_1 –C_6 alkyl-CO_2 —R^{95}, C_1 –C_6 fluoroalkoxy, NO_2, NR^{96} R^{97}, and $NHCOR^{98}$;
R^{85} to R^{89} are independently chosen from the group consisting of hydrogen and C_1 –C_6 alkyl;
or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[000133] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:
—A^5=A^6—A^7=A^8— is selected from the group consisting of:
(a) —CH=CH—CH=CH—,
(b) —CH_2 —CH_2 —CH_2 —C(O)—, —CH_2 —CH_2 —C(O)—CH_2 —, —CH_2 —C(O)—CH_2 —CH_2, —C(O)—CH_2 —CH_2 —CH_2,
(c) —CH_2 —CH_2 —C(O)—, —CH_2 —C(O)—CH_2 —, —C(O)—CH_2 —CH_2 —
(d) —CH_2 —CH_2 —O—C(O)—, CH_2 —O—C(O)—CH_2 —, —O—C(O)—CH_2 —CH_2 —,

(e) —CH_2 —CH_2 —C(O)—O—, —CH_2 —C(O)—OCH_2 —, —C(O)—O—CH_2 —CH_2 —,

(f) —$C(R^{105})_2$ —O—C(O)—, —C(O)—O—$C(R^{105})_2$ —, —O—C(O)—$C(R^{105})_2$ —, —$C(R^{105})_2$ —C(O)—O—,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,

(i) —CH=CH—N=CH—,

(j) —CH=CH—CH=N—,

(k) —N=CH—CH=N—,

(l) —N=CH—N=CH—,

(m) —CH=N—CH=N—,

(n) —S—CH=N—,

(o) —S—N=CH—,

(p) —N=N—NH—,

(q) —CH=N—S—, and

(r) —N=CH—S—;

R^{99} is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2NH_2$, $S(O)_2NHCOCF_3$, $S(O)(NH)CH_3$, $S(O)(NH)NH_2$, $S(O)(NH)NHCOCF_3$, $P(O)(CH_3)OH$, and $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_1 –C_6 alkyl,

(b) C_3 –C_7 cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —C(R^{103})(R^{104})—OH,

(12) —C(R^{103})(R^{104})—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{106};

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —C(R^{103})(R^{104})—OH, and

(10) —C(R^{103})(R^{104})—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of –A^5=A^6—A^7=A^8— and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, C(R^{103})(R^{104})OH,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^3,

(2) —O—C_1 –C_5 alkyl-Q^3,

(3) —S—C_1 –C_5 alkyl-Q^3,

(4) —C_1 –C_3 alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_1 –C_3 alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_1 –C_5 alkyl-O—Q^4,

(7) —C_1 –C_5 alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_1 –C_3 alkyl, and Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O$—C_1 –C_4 alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of hydrogen and C_1 –C_6 alkyl; or

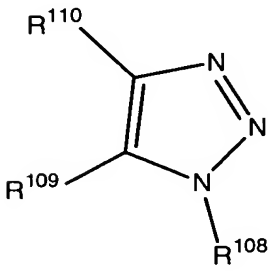
R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_1 –C_6 alkyl;

R^{107} is hydrogen, C_1 –C_6 alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, —$C(R^{107})$=$C(R^{107})$—; —$C(R^{107})$=N—; or —N=$C(R^{107})$—.

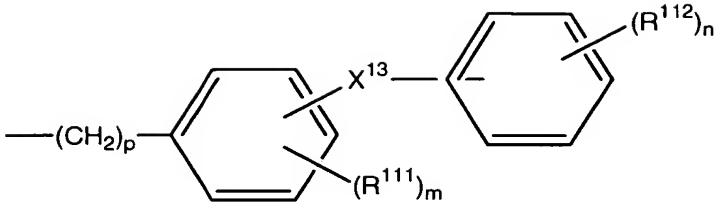
[000134] Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:



wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5;

X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

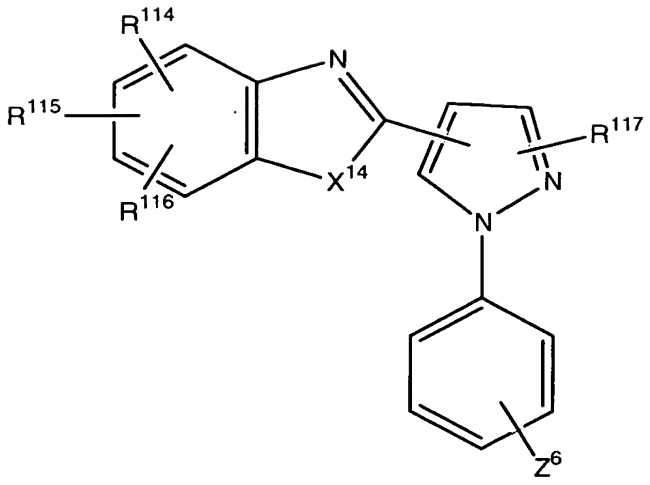
R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl;

R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl;

wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

[000135] Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen;

R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl or lower alkanoyloxy;

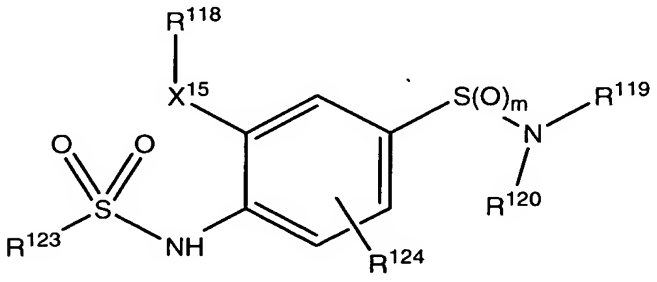
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

[000136] Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

R^{124} denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121}, or a polyfluoroalkyl group;

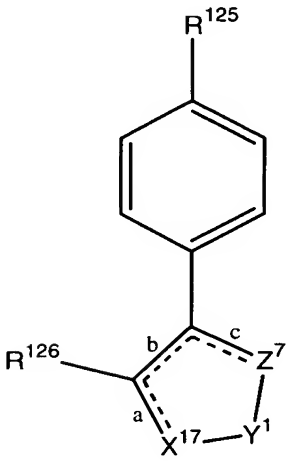
R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

[000137] Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in U.S.

Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) —CH_2 CH_2 CH_2 —,

(b) —C(O)CH_2 CH_2 —,

(c) —CH_2 CH_2 C(O)—,

(d) —CR^{129} ($R^{129'}$)—O—C(O)—,

(e) —C(O)—O—CR^{129} ($R^{129'}$)—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR^{128} =N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R^{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$;

when side b is a double bond, and sides a and c are single bonds; and

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2$ CH_3,

(b) $S(O)_2$ NH_2,

(c) $S(O)_2$ $NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_1 –C_6 alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{129})(R^{130})$—OH,

(12) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{129} ;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) hydroxyl C_1 –C_6 alkyl,

(f) —C(O)— C_1 –C_6 alkyl,

(g) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —C_1 –C_5 alkyl-O—C_1 –C_3 alkyl-Q^5,

(3) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(4) —C_1 –C_5 alkyl-O—Q^5, or

(5) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) –Q^5,

(f) —O—Q^5;

(g) —S—Q^5, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —O—C_1 –C_5 alkyl-Q^5,

(3) —S—C_1 –C_5 alkyl-Q^5,

(4) —C_1 –C_3 alkyl-O—C_1 –C_3 alkyl-Q^5,

(5) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(6) —C_1 –C_5 alkyl-O—Q^5,

(7) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

(b) C_1 –C_6 alkyl;

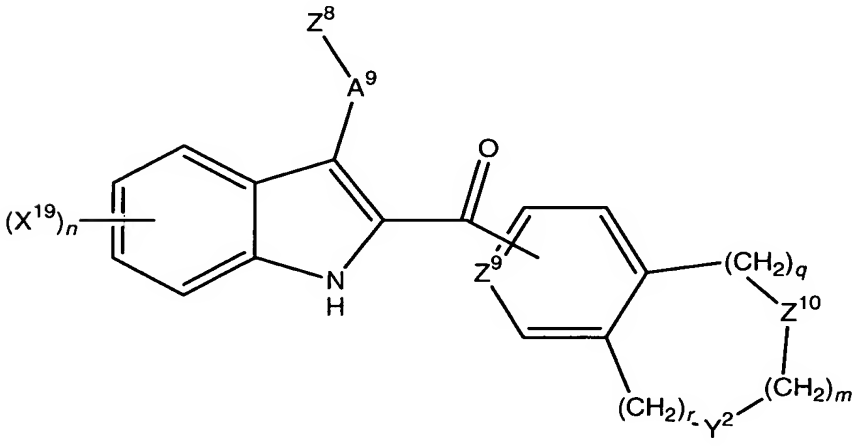
or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2H, CO_2—C_1 –C_4 alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})(O—C_1$ –C_4 alkyl);

provided that when X—Y—Z is —S—CR^{128}=$CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[000138] An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

[000139] Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein:

A^9 is C_1 –C_6 alkylene or —NR^{133} —;

Z^8 is $C(=L^3)R^{134}$, or SO_2R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2 —, O, S and —N—R^{133};

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkoxy, C_1 –C_4 alkylthio, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

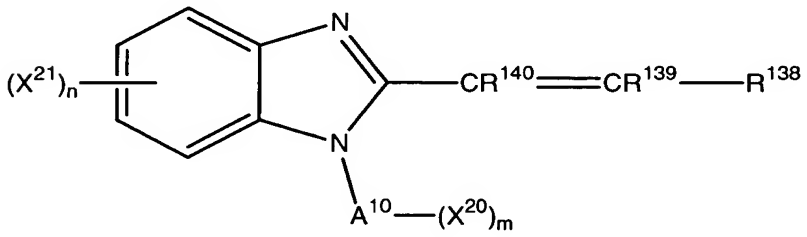
R^{133} is hydrogen or C_1 –C_4 alkyl;

R^{134} is hydroxyl, C_1 –C_6 alkyl, halo-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, halo-substituted C_1 –C_6 alkoxy, C_3 –C_7 cycloalkoxy, C_1 –C_4 alkyl(C_3 –C_7 cycloalkoxy), —NR^{136} R^{137}, C_1 –C_4 alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy and nitro;

R^{135} is C_1 –C_6 alkyl or halo-substituted C_1 –C_6 alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, $C_{1\text{-}6}$ alkyl and halo-substituted C_1 –C_6 alkyl.

[000140] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and
said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amonio, N-(C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 –C_4 alkyl)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-(C_1 –C_4 alkyl)-N-(C_1 –C_4 alkanoyl) amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)hydroxyl, cabamoyl, [N-(C_1 –C_4 alkyl) amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

R^{138} is selected from:

hydrogen;

straight or branched C_1 –C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from

halo, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, □ydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-[C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)]amino, N-[(C_1 –C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 –C_4 alky)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from:

hydrogen;

halo;

C_1 –C_4 alkyl;

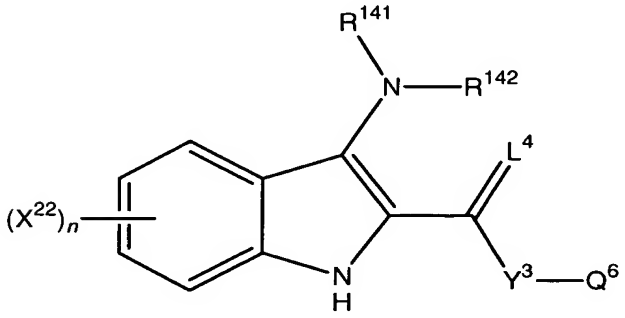
phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

[000141] Compounds that may be employed as a Cox-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof, wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_1 –C_4 alkylidene;

Q^6 is:

(a) C_1 –C_6 alkyl or halosubstituted C_1 –C_6 alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkoxy, amino and mono- or di-(C_1 –C_4 alkyl)amino,

(b) C_3 –C_7 cycloalkyl optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkyl and C_1 –C_4 alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, $S(O)_m$ R^{143}, SO_2 NH_2, SO_2 $N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, $NHC(O)R^{143}$, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_1 –C_4 alkyl, CF_3, hydroxyl, OR^{143}, $S(O)_mR^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, C_1 –C_4 alkyl-OH, $S(O)_m$ R^{143}, SO_2 NH_2, SO_2 $N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, $NHC(O)R^{143}$, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, OCF_3, SR^{143}, SO_2 CH_3, SO_2 NH_2, amino, C_{1-4} alkylamino and $NHSO_2$ R^{143};

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_1 –C_6 alkyl optionally substituted with a substituent selected independently from hydroxyl, OR^{143}, nitro, amino, mono- or di-(C_1

$-C_4$ alkyl)amino, CO_2H, CO_2 (C_1 $-C_4$ alkyl), $CONH_2$, $CONH(C_1$ $-C_4$ alkyl) and $CON(C_1$ $-C_4$ alkyl$)_2$;

R^{142} is:

(a) hydrogen,

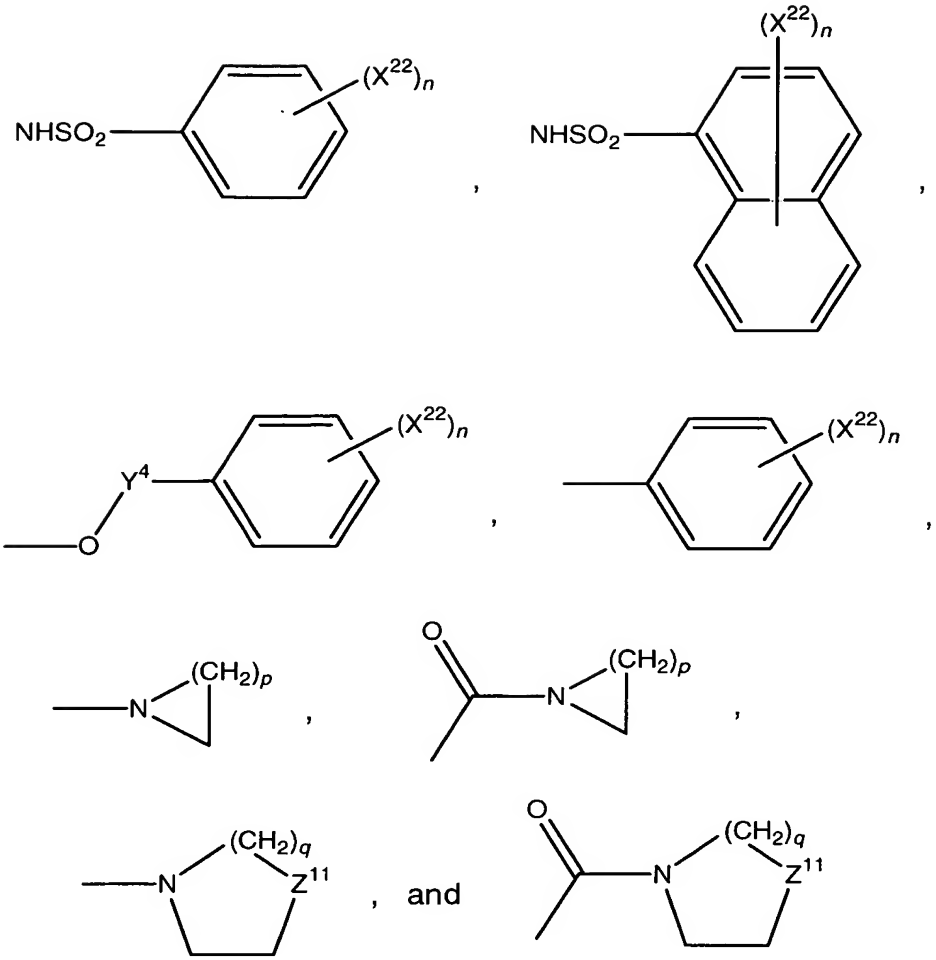
(b) C_1 $-C_4$ alkyl,

(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_1 $-C_{22}$ alkyl or C_2 $-C_{22}$ alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:

(c-1-1) halo, hydroxyl, OR^{143}, $S(O)_m R^{143}$, nitro, amino, mono- or di-(C_1 $-C_4$ alkyl)amino, $NHSO_2 R^{143}$, CO_2H, CO_2 (C_1 $-C_4$ alkyl), $CONH_2$, $CONH(C_1$ $-C_4$ alkyl), $CON(C_1$ $-C_4$ alkyl$)_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulas:



(c-2) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) –Y^5—C_3 –C_7 cycloalkyl or –Y^5—C_3 –C_7 cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_1 –C_4 alkyl, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

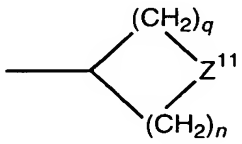
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, halosubstituted C_1 –C_8 alkyl, halosubstituted C_1 –C_8 alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_1$ –C_4 alkyl), $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, C_1 –C_4 alkylamino, di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, CO_2 H and CO_2 (C_1 –C_4 alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstitutued C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, nitro, halosubstitutued C_1 –C_4 alkyl, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkylOR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl) or $CON(C_1$ –C_4 alkyl)$_2$;

R^{143} is C_1 –C_4 alkyl or halosubstituted C_1 –C_4 alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_1 –C_6 alkyl, halosubstitutued C_1 –C_4 alkyl or –Y^5-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CF_3, OCF_3, CN and nitro;

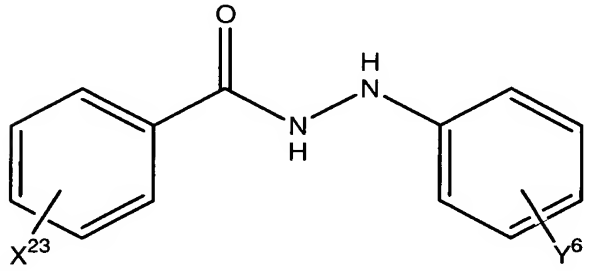
with the proviso that a group of formula –Y^5—Q is not methyl or ethyl when X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[000142] Aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869 can serve as Cox-2 selective inhibitors of the present invention. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:



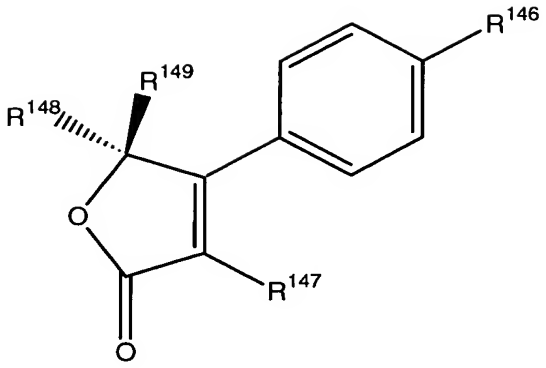
XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl;

or a pharmaceutically acceptable salt thereof,.

[000143] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof, wherein:

R^{146} is selected from the group consisting of SCH_3, —$S(O)_2$ CH_3 and —$S(O)_2$ NH_2 ;

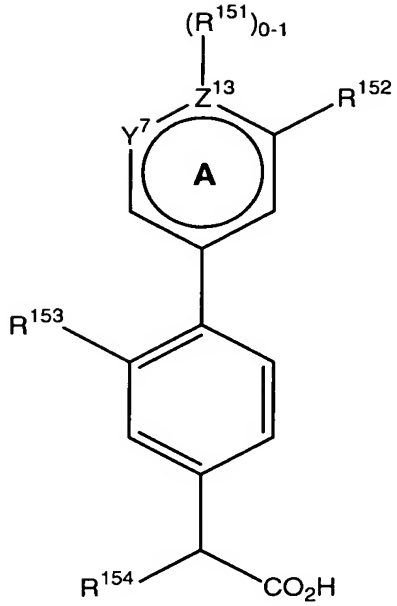
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[000144] Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable configuration planar with ring A to within about 15 degrees;

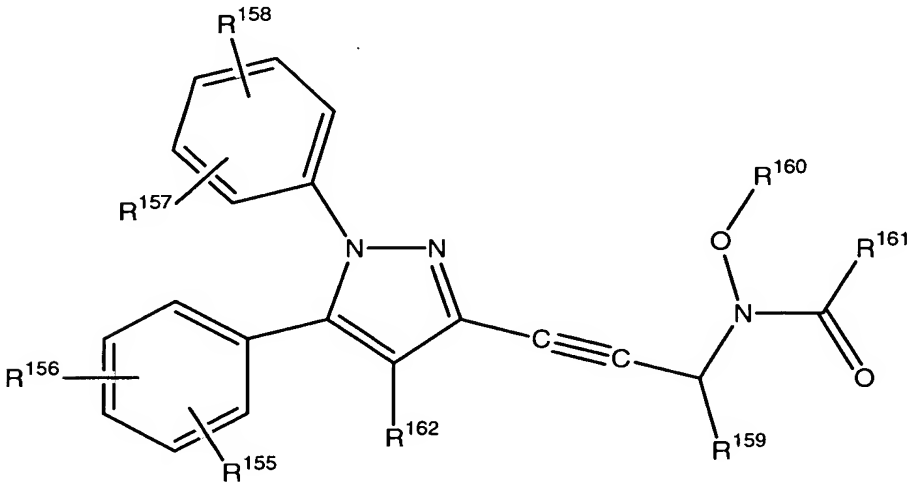
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_1 –C_2 alkyl, —OC_1 –C_2 alkyl, —NHC_1 –C_2 alkyl, —$N(C_1$ –C_2 alkyl$)_2$, —C(O) C_1 –C_2 alkyl, —S—C_1 –C_2 alkyl and —C(S) C_1 –C_2 alkyl;

Y^7 represents N, CH or C—OC_1 –C_3 alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[000145] Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_1 –C_5 alkyl, C_1 –C_5 alkoxy, phenyl, halo, hydroxyl, C_1 –C_5 alkylsulfonyl, C_1 –C_5 alkylthio, trihaloC_1 –C_5 alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_1 –C_5 alkyl, trihaloC_1 –C_5 alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

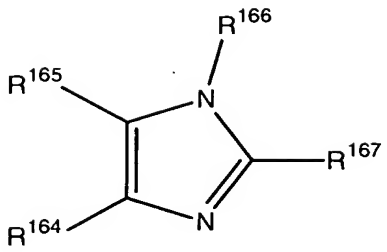
R^{160} is hydrogen, C_1 –C_5 alkyl, phenyl C_1 –C_5 alkyl, substituted phenyl C_1 –C_5 alkyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro, or R^{160} is C_1 –C_5 alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro;

R^{161} is C_1 –C_{10} alkyl, substituted C_1 –C_{10} alkyl where the substituents are halogen, trihaloC_1 –C_5 alkyl, C_1 –C_5 alkoxy, carboxy, C_1 –C_5 alkoxycarbonyl, amino, C_1 –C_5 alkylamino, diC_1 –C_5 alkylamino, diC_1 –C_5 alkylaminoC_1 –C_5 alkylamino, C_1 –C_5 alkylaminoC_1 –C_5 alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_1 –C_5 alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_1 –C_5 alkyl, halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and $C_{1\text{-}5}$ alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_1 –C_5 alkyl; R^{162} is hydrogen, C_1 –C_5 alkyl, nitro, amino, and halogen;

and pharmaceutically acceptable salts thereof.

[000146] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl and halogen, or

substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, 2-(trimethylsilyl)ethoxymethyl), C_1 –C_5 alkoxycarbonyl, aryloxycarbonyl, arylC_1 –C_5 alkyloxycarbonyl, arylC_1 –C_5 alkyl, phthalimidoC_1 –C_5 alkyl, aminoC_1 –C_5 alkyl, diaminoC_1 –C_5 alkyl, succinimidoC_1 –C_5 alkyl, C_1 –C_5 alkylcarbonyl, arylcarbonyl, C_1 –C_5 alkylcarbonylC_1 –C_5 alkyl, aryloxycarbonylC_1 –C_5 alkyl, heteroarylC_1 –C_5 alkyl where the heteroaryl contains 5 to 6 ring atoms, or

substituted arylC_1 –C_5 alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, C_1 –C_5 alkoxy, halogen, amino, C_1 –C_5 alkylamino, and diC_1 –C_5 alkylamino;

R^{167} is $(A^{11})_n$–$(CH^{165})_q$–X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxyl, halogen, vinyl, ethynyl, C_1 –C_5 alkyl, C_3 –C_7 cycloalkyl, C_1 –C_5 alkoxy, phenoxy, phenyl, arylC_1 –C_5 alkyl, amino, C_1 –C_5 alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylthio, C_1 –C_5 alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, araC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_1 –C_5 alkyl,

wherein the substituents are selected from the group consisting of one or more C_1 –C_5 alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC_1 –C_5 alkyl,

wherein the alkyl substituent is hydroxyl,

substituted arylC_1 –C_5 alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, arylC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted C_1 –C_5 alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_1 –C_5 alkoxy and trifluoromethyl,

with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_1 –C_2 alkyl;

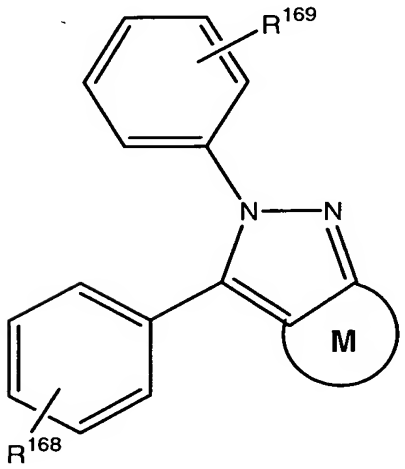
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not 2-(trimethylsilyl)ethoxymethyl;

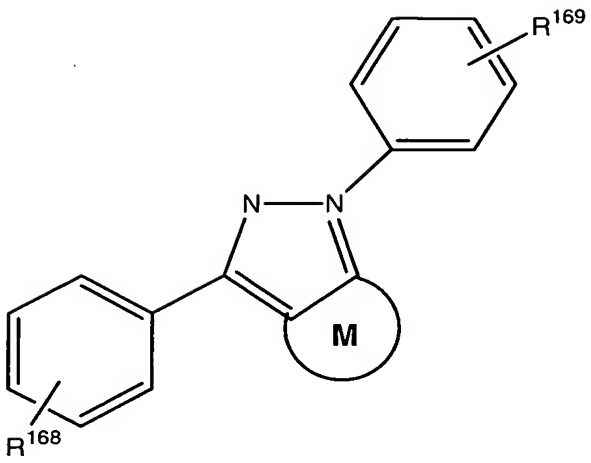
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

[000147] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



XXXIII

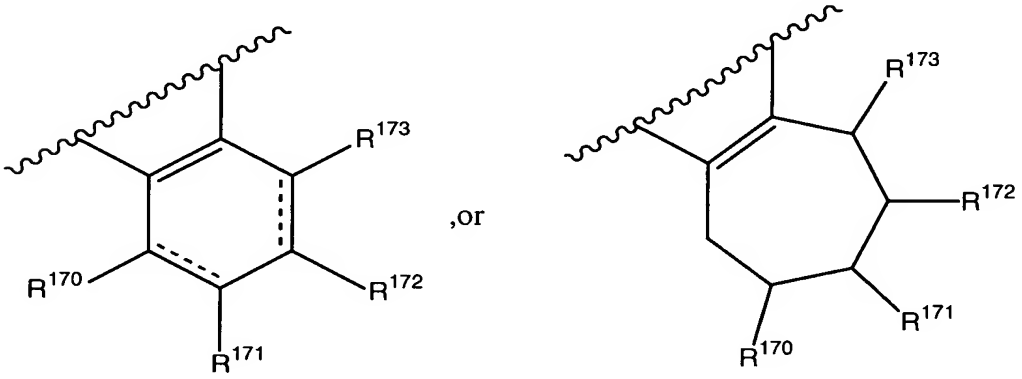


XXXIV

wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy, nitro, amino, □ydroxyl, trifluoro, —S(C_1 –C_6)alkyl, —SO(C_1 –C_6)alkyl and —SO_2 (C_1 –C_6)alkyl; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



wherein:

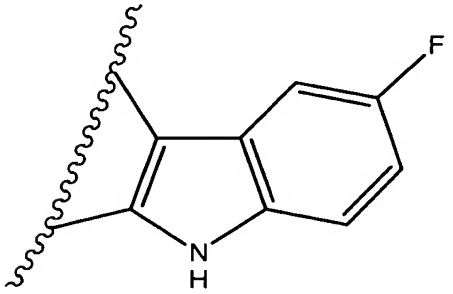
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH= and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 –C_6)alkyl and di(C_1 –C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino, (C_1 –C_6)alkyl and (C_1 –C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 –C_6)alkyl; and

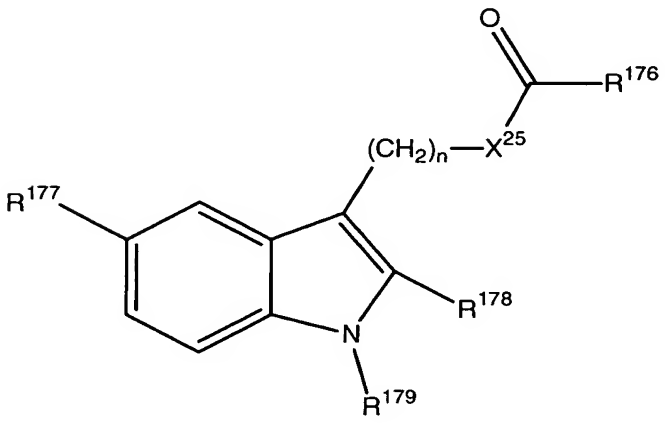
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 –C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that

if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[000148] Esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890 can serve as Cox-2 selective inhibitors of the present invention. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_1 –C_6 hydroxyalkyl, branched C_1 –C_6 hydroxyalkyl, hydroxyl substituted C_4 –C_8 aryl, primary, secondary or tertiary C_1 –C_6 alkylamino, primary, secondary or tertiary branched C_1 –C_6 alkylamino, primary, secondary or tertiary C_4 –C_8 arylamino, C_1 –C_6 alkylcarboxylic acid, branched C_1 –C_6 alkylcarboxylic acid, C_1 –C_6 alkylester, branched C_1 –C_6 alkylester, C_4 –C_8 aryl, C_4 –C_8 arylcarboxylic acid, C_4 –C_8 arylester, C_4 –C_8 aryl substituted C_1 –C_6 alkyl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_4 –C_8 aryl, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, C_1 –C_6 branched alkoxy, C_4 –C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

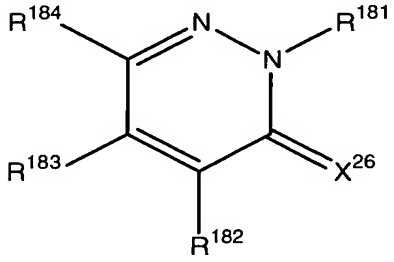
R^{178} is hydrogen, C_1 –C_6 alkyl or C_1 –C_6 branched alkyl;

R^{179} is C_1 –C_6 alkyl, C_4 –C_8 aroyl, C_4 –C_8 aryl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 –C_8 aroyl, or alkyl-substituted C_4 –C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 –C_6 or C_1 –C_6 branched alkyl.

[000149] Materials that can serve as a Cox-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^a, and –$NNR^b R^c$;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl,

cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, $—(CH_2)_n C(O)R^{186}$, $—(CH_2)_n CH(OH)R^{186}$, $—(CH_2)_n C(NOR^d)R^{186}$, $—(CH_2)_n CH(NOR^d)R^{186}$, $—(CH_2)_n CH(NR^d R^e)R^{186}$, $—R^{187} R^{188}$, $—(CH_2)_n C\equiv CR^{188}$, $—(CH_2)_n [CH(CX^{26'}{}_3)]_m (CH_2)_p R^{188}$, $—(CH_2)_n (CX^{26'}{}_2)_m (CH_2)_p R^{188}$, and $—(CH_2)_n (CHX^{26'})_m (CH_2)_m R^{188}$;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

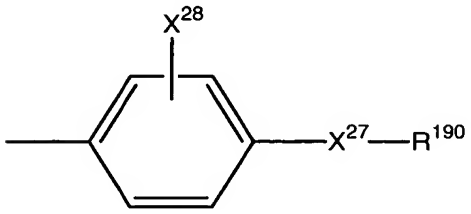
n is an integer from 0-10;

p is an integer from 0-10;

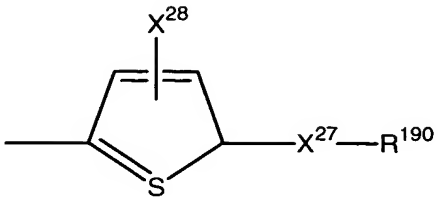
R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:



and



X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}\ R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

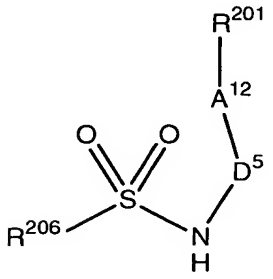
R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

Y^8 is selected from the group consisting of –OR^{195}, —SR^{195}, —$C(R^{197})(R^{198})R^{195}$, —$C(O)R^{195}$, —$C(O)OR^{195}$, —$N(R^{197})C(O)R^{195}$, —$NC(R^{197})R^{195}$, and —$N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}\ R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[000150] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the present invention. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



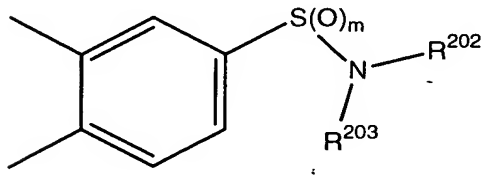
XXXVII

wherein:

A^{12} denotes oxygen, sulphur or NH;

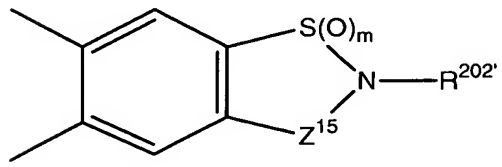
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n -X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one

or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n -X^{29}$, $R^{202,}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n -X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, —OR^{204}, —COR^{204}, —$CO_2 R^{204}$, —$OCO_2 R^{204}$, —CN, —$CONR^{204} OR^{205}$, —$CONR^{204} R^{205}$, —SR^{204}, —$S(O)R^{204}$, —$S(O)_2 R^{204}$, —$NR^{204} R^{205}$, —$NHC(O)R^{204}$, —$NHS(O)_2 R^{204}$;

Z^{15} denotes $-CH_2$ —, —CH_2 $-CH_2$ —, —CH_2 $-CH_2$ $-CH_2$ —, —CH_2 –CH=CH—, —CH=CH—CH_2 —, —CH_2 —CO—, —CO—CH_2 —, —NHCO—, —CONH—, —$NHCH_2$ —, —CH_2 NH—, —N=CH—, —NHCH—, —CH_2–CH_2—NH—, —CH=CH—, >N—R^{203}, >C=O, $>S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

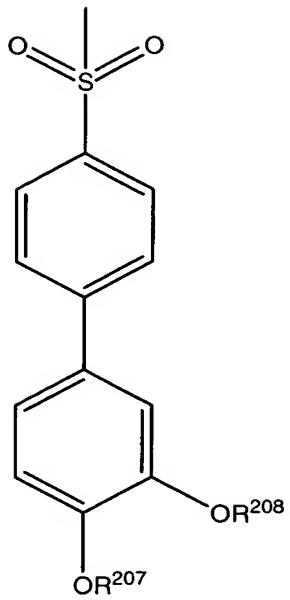
R^{206} is a straight-chained or branched C_1 –C_4 alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

[000151] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl derivatives have the formula shown below in formula **XXXX**:



XXXX

wherein:

R^{207} and R^{208} are respectively a hydrogen;

C_1 –C_4-alkyl substituted or not substituted by halogens;

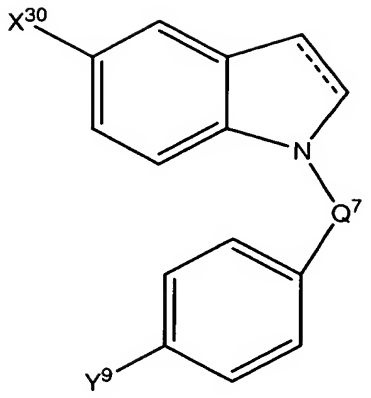
C_3 –C_7-cycloalkyl;

C_1 –C_5-alkyl containing 1-3 ether bonds and/or an aryl substitute;

substituted or not substituted phenyl;

or substituted or not substituted five or six ring-cycled heteroaryl containing more than one hetero atoms selected from a group consisting of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one- or multi-substituted by a substituent selected from a group consisting of hydrogen, methyl, ethyl, and isopropyl).

[000152] Cox-2 selective inhibitors such as 1H-indole derivatives described in U.S. Patent No. 6,599,929 are useful in the present invention. Such 1H-indole derivatives have the formula shown below in formula **XXXXI**:



XXXXI

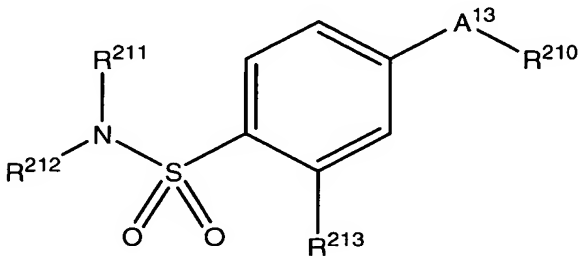
wherein:

X^{30} is $-NHSO_2R^{209}$ wherein R^{209} represents hydrogen or C_1 $-C_3$–alkyl;

Y^9 is hydrogen, halogen, C_1 $-C_3$–alkyl substituted or not substituted by halogen, NO_2, NH_2, OH, OMe, CO_2H, or CN; and

Q^7 is C=O, C=S, or CH_2.

[000153] Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula **XXXXII**:



XXXXII

wherein:

A^{13} is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein A^{13} is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl,

heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

R^{210} is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein R^{210} is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} is selected from hydrido and alkoxycarbonylalkyl;

R^{212} is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided A^{13} is not tetrazolium, or pyridinium; and further provided A^{13} is not indanone when R^{212} is alkyl or carboxyalkyl; further provided A^{13} is not thienyl, when R^{210} is 4-fluorophenyl, when R^{211} is hydrido, and when R^{212} is methyl or acyl; and

R^{213} is hydrido;

or a pharmaceutically-acceptable salt thereof.

[000154] Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]propanamide;

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]butanamide;

N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide ;
2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H pyrazol-1-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;

N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-[[.sup.4 -(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
2-(acetylamino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-oxobutanoate;
methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;
N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;
methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;

4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenezenesulfonamide;
N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;
N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benezenesulfonamide;
N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide:
N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)phenyl]sulfonyl]acetamide;
4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;
N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl]phenyl]sulfonyl]propanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;
4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenezenesulfonamide; and
N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.

[000155] Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XXXXII** wherein:

A^{13} is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;

R^{210} is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl,

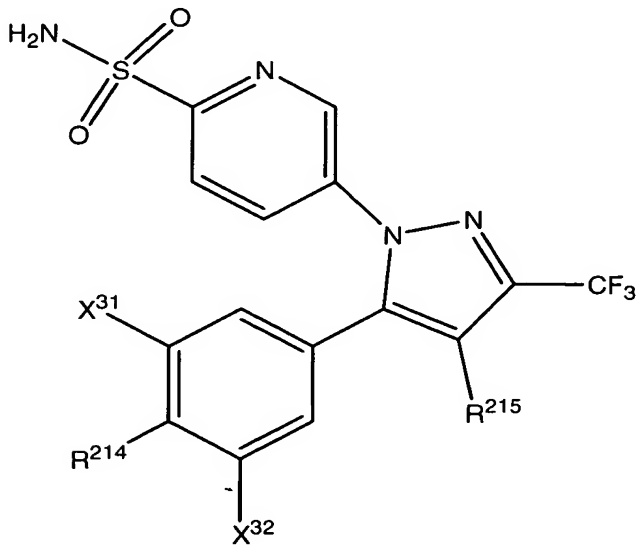
hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} and R^{212} are independently selected from the group consisting of hydroxyalkyl and hydrido but at least one of R^{211} and R^{212} is other than hydrido; and

R^{213} is selected from the group consisting of hydrido and fluoro.

[000156] Examples of prodrug compounds disclosed in U.S. 6,613,790 that are useful as Cox-2 inhibitors of the present invention include, but are not limited to, N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1- yl]benzenesulfonamide, N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyraz ol-1-yl]benzenesulfonamide, or pharmaceuticaly-acceptable salts thereof.

[000157] Cox-2 selective inhibitors such as sulfamoylheleroaryl pyrazole compounds that are described in U.S. Patent No. 6,583,321 may serve as Cox-2 inhibitors of the present invention. Such sulfamoylheleroaryl pyrazole compounds have the formula shown below in formula **XXXXIII**:



XXXXIII

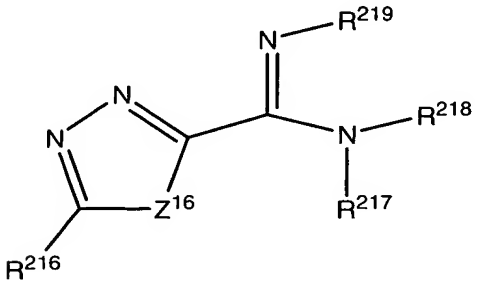
wherein:

R^{214} is furyl, thiazolyl or oxazolyl;

R^{215} is hydrogen, fluoro or ethyl; and

X^{31} and X^{32} are independently hydrogen or chloro.

[000158] Heteroaryl substituted amidinyl and imidazolyl compounds such as those described in U.S. Patent No. 6,555,563 are useful as Cox-2 selective inhibitors of the present invention. Such heteroaryl substituted amidinyl and imidazolyl compounds have the formula shown below in formula **XXXXIV**:



XXXXIV

wherein:

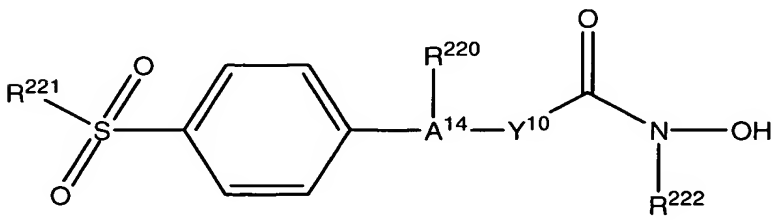
Z^{16} is O or S,

R^{216} is optionally substituted aryl,

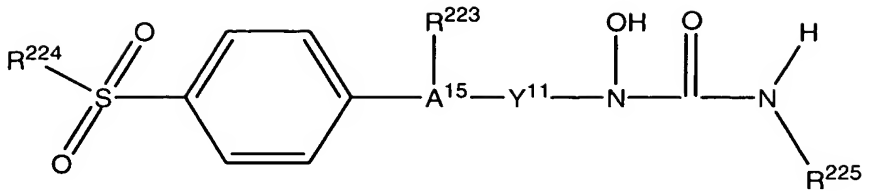
R^{217} is aryl optionally substituted with aminosulfonyl, and

R^{218} and R^{219} cooperate to form an optionally substituted 5-membered ring.

[000159] Materials that can serve as Cox-2 selective inhibitors of the present invention include substituted hydroxamic acid derivatives that are described in U.S. Patent Nos. 6,432,999, 6,512,121, and 6,515,014. These compounds also act as inhibitors of the lipoxygenase-5 enzyme. Such substituted hydroxamic acid derivatives have the general formulas shown below in formulas **XXXXV** and **XXXXVI**:



XXXXV



XXXXVI

[000160] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is selected from lower alkenylene and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000161] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkylene, lower alkenylene and lower alkynylene;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

[000162] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is a ring substiuent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A^{14} is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is lower alkylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is otionallv substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000163] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarboryl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitto, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000164] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position

with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000165] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XXXXV**, wherein:

A^{15} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

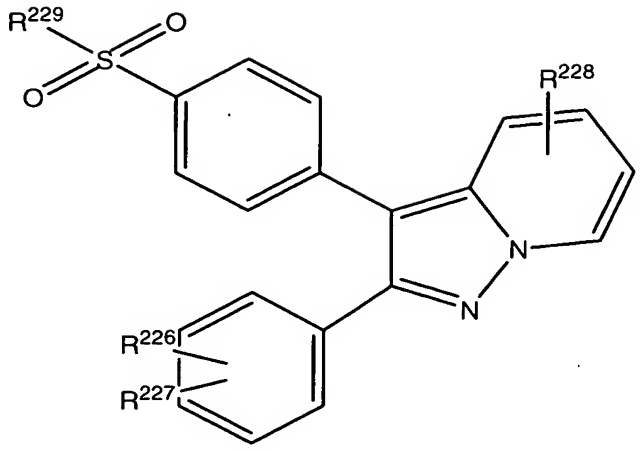
Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000166] Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the formula shown below in formula **XXXXVII**:



XXXXVII

wherein:

R^{226} and R^{227} are independently selected from the group consisting of H, halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms;

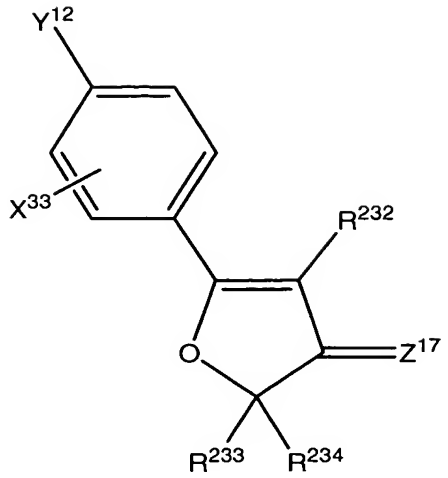
R^{228} is halogen, CN, CON R^{230} R^{231}, CO_2 H, CO_2 C_1 –C_6 alkyl, or $NHSO_2R^{230}$;

R^{229} is C_1 –C_6 alkyl or NH_2 ; and

R^{225} and R^{225} are independently selected from the group consisting of H, C_1 –C_6 alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms,

or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

[000167] Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula **XXXXVIII**:



XXXXVIII

wherein:

X^{33} represents halo, hydrido, or alkyl;

Y^{12} represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

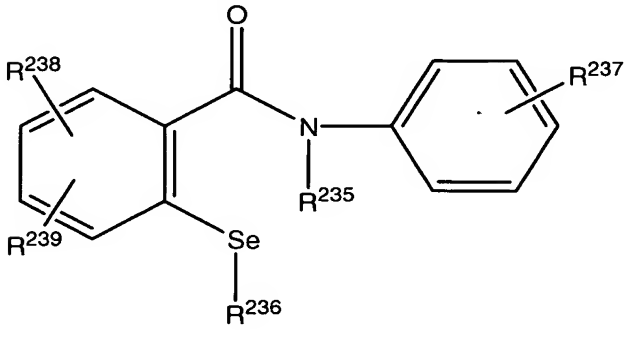
Z^{17} represents oxygen or sulfur atom;

R^{233} and R^{234} are selected independently from lower alkyl radicals;

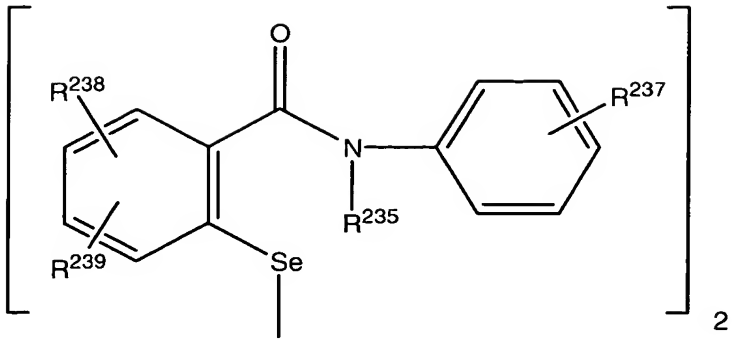
and R^{232} represents a substituted or non-substituted aromatic group of 5 to 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[000168] Cox-2 selective inhibitors that can be used in the present invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives that are described in U.S. Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives have the formulas shown below in formulas **XXXXIX** or **XXXXIX'**:



XXXXIX



XXXXIX'

wherein:

R^{235} is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

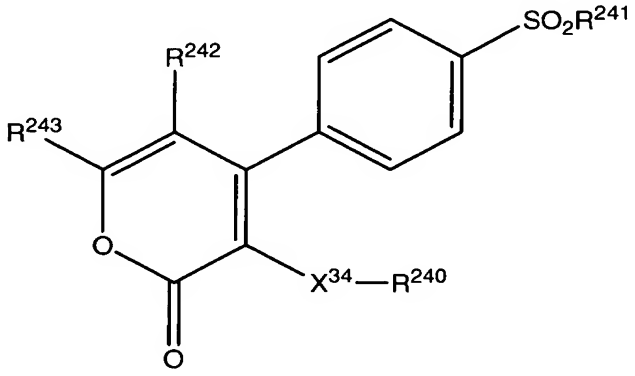
R^{236} is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or R^{235} and R^{236} are joined to each other by a single bond;

R^{237} is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxyl group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

R^{238} and R^{239} are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxyl group having 1-4 carbon atoms, a trifluoromethyl group, or R^{238} and R^{239} are joined to each other to form a methylenedioxy group,

a salt thereof, or a hydrate thereof.

[000169] Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **XXXXX:**



XXXXX

wherein:

X^{34} is selected from the group consisting of:

(a) a bond,

(b) --$(CH_2)_m$ --, wherein m 1 or 2,

(c) --C(O)--,

(d) --O--,

(e) --S--, and

(f) --$N(R^{244})$--;

R^{240} is selected from the group consisting of:

(a) C_1 –C_{10} alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: hydroxy, halo, C_1 –C_{10} alkoxy, C_1 – C_{10} alkylthio, and CN,

(b) phenyl or naphthyl, and

(c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5 atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3 additional N atoms; or

a monocyclic ring of 6 atoms having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c) above are each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, C_1 –C_{10} alkoxy, C_1 –C_{10} alkylthio, CN, C_1 –C_{10} alkyl, optionally substituted to its maximum with halo, and N_3 ;

R^{241} is selected from the group consisting of

(a) C_1 –C_6 alkyl, optionally substituted to its maximum with halo,

(b) NH_2, and

(c) $NHC(O)C_1$ –C_{10} alkyl, optionally substituted to its maximum with halo;

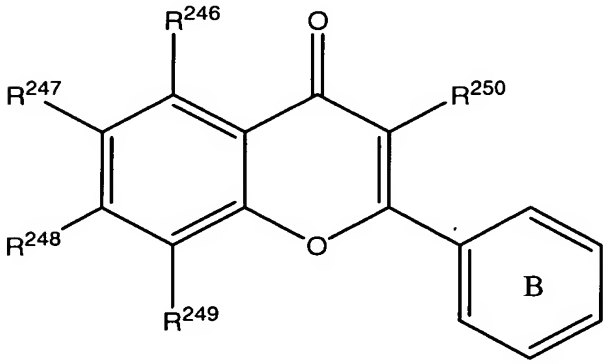
R^{242} and R^{243} are each independently selected from the group consisting of: hydrogen, halo, and C_1 –C_6 alkyl, optionally substituted to its maximum with halo; and

R^{244} is selected from the group consisting of: hydrogen and C_1 –C_6 alkyl, optionally substituted to its maximum with halo.

[000170] Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:

4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,
3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl)-3-phenylthio-6-trifluoromethyl-pyran-2-one,
3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one,
and
3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

[000171] Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present invention. Such free-B-ring flavanoids have the general structure shown in formula **XXXXXI**:



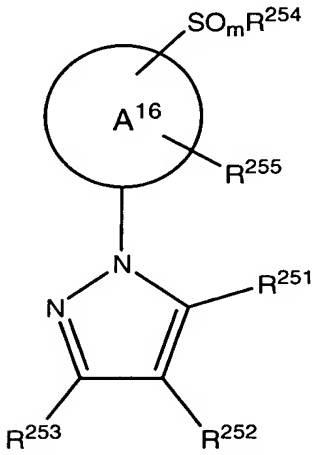
XXXXXI

wherein:

R^{246}, R^{247}, R^{248}, R^{249}, and R^{250} are independently selected from the group consisting of: --H, --OH, --SH, --OR, --SR, $--NH_2$, $--NHR^{245}$, $--N(R^{245})_2$,

--$N(R^{245})_3{}^+X^{35-}$, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein R^{245} is an alkyl group having between 1-10 carbon atoms; and X^{35} is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

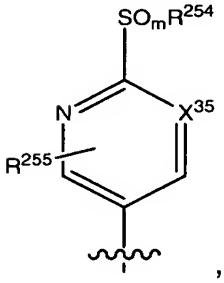
[000172] Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **XXXXXII**:



XXXXXII

or a pharmaceutically acceptable salt thereof, wherein:

the ring of the formula (R^{255})-A-(SO_mR^{254}) is selected from the group consisting of:



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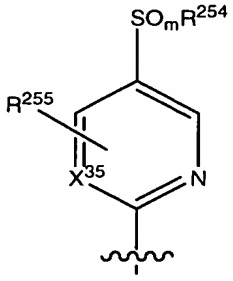

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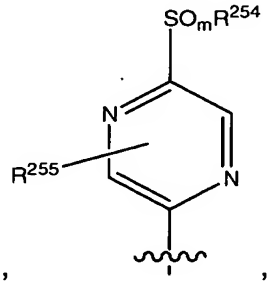

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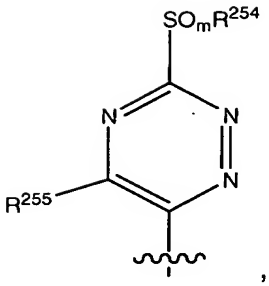

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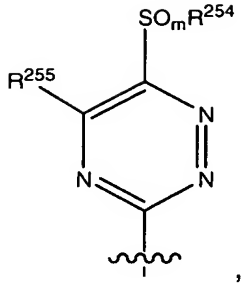

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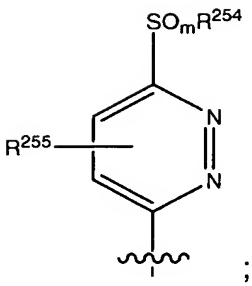


;

m is 0, 1 or 2;

X^{35} is $>CR^{255}$ or >N;

R^{251} is a radical selected from the group consisting of H, NO_2, CN, (C_1 – C_6)alkyl, (C_1 –C_6)alkyl-SO_2-, (C_6 –C_{10})aryl-SO_2-, H-(C=O)-, (C_1 –C_6)alkyl-(C=O)-, (C_1 –C_6)alkyl-)-(C=O)-, (C_1 –C_9)heteroaryl-(C=O)-, (C_1 – C_9)heterocyclyl-(C=O)-, H_2N-(C=O)-, (C_1 –C_6)alkyl-NH-(C=O)-, [(C_1 – C_6)alkyl]$_2$-N-(C=O)-, [(C_6 –C_{10})aryl]$_2$-NH-(C=O)-, [(C_1 –C_6)alkyl]-[((C_6 – C_{10})aryl-N]-(C=O)-, HO-NH-(C=O)-, and (C_1 –C_6)alkyl-O-NH-(C=O)-;

R^{252} is a radical selected from the group consisting of H, -NO_2, -CN, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_9)heterocyclyl, (C_1-C_6)alkyl-O-, (C_3-C_7)cycloalkyl-O-, (C_6-C_{10})aryl-O-, (C_1 -C_9)heteroaryl-O-, (C_6 -C_9)heterocyclyl-O-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_3-C_7)cycloalkyl-(C=O)-, (C_6-C_{10})aryl-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_7)cycloalkyl-O-(C=O)-, (C_6-C_{10})aryl-O-(C=O)-, (C_1-C_9)heteroaryl-O-(C=O)-, (C_1-C_9)heterocyclyl-O-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_7)cycloalkyl-(C=O)-O-, (C_6-C_{10})aryl-(C=O)-O-, (C_1-C_9)heteroaryl-(C=O)-O-, (C_1-C_9)heterocyclyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_7)cycloalkyl-(C=0)-NH-, (C_6-C_{10}aryl-(C=O)-NH-. (C_1-C_9)heteroaryl-(C=O)-NH-, (C_1-C_9)heterocyclyl-(C=O)-NH-, (C_1-C_6)alkyl-O-(C=O)-NH-, (C_1-C_6)alkyl-NH, [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-. [(C_3-C_7)cycloalkyl]$_2$-N-, [(C_6-C_{10})aryl]-NH-, [(C_6-$C_{1\,0}$)aryl]$_2$-N-, [(C_1 –C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, [(C_1 -C_9)heteroaryl]-NH-, [(C_1-C_9)heteroaryl]$_2$-N-, [(C_1-C_9)heterocycly]-NH-, [(C_1-C_9)heterocyclyl]$_2$-N-, H_2N-(C=O)-, HO-NH-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_3-C_7)cycloalkyl]-NH-(C=O)-, [(C_3-C_7)cycloalkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-

(C=O)-, [(C_6-C_{10}aryl]$_2$-N-(C=O)-, [(C_1-C $_6$)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, [(C_1-C_9)heteroaryl]-NH-(C=O)-, [(C_1-C_9)heferoaryl]$_2$-N-(O=O)-, [(C_1-C_9)heterocyclyl]-NH-(C=O)-, (C_1–C_6)alkyl-S- and (C_1-C_6)alkyl optionally substituted by one -OH substituent or by one to four fluoro substituents;

R^{253} is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical orsaid saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally contain one to four ring heteroatoms independently selected Irom the groups consisting of -N=, -NH-, -O-. and -S-;

wherein said saturated (3- to 4-membered)-heterooyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-nembered)-heterocyclyl ring radical; may optionally be substituted on any ring carbon atom by one to three substituents per ring independently selected from the group consisting of halo, -OH, -CN, -NO_2, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)hetorocyclyl, (C_1 –C_6)alkyl-O-, H-(C=0)-, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, -NH_2, (C_1-C_6)alkyl-NH-, [(C_1-C_6) alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-[(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-HN-, (C_1-C_6)alkyl-(C=O)-[(C_1-C_6)alkyl-N]-, -SH, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-(S=0)-, (C_1-C_6)alkyl-SO_2- and (C_1-C_6)alkyl optionally substituted with one to fourfluoro moieties;

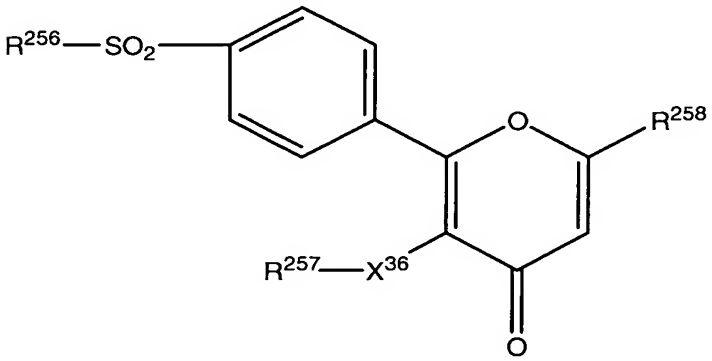
wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of (C_3-C_7)cyoloalkyl, (C_6-C_{10})aryl, (C_2-

C_9)heterocyclyl, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1 –C_6)alkyl-O-NH-(C=O)-, and (C_1-C_6)alkyl optionally substituted with one to four fluoro moieties;

R^{254} is an (C_1-C_6)alkyl radical optionally substituted by one to four fluoro substituents; and

R^{255} is a radical selected from the group consisting of H, halo, -OH, (C_1-C_6)alkyl-O-, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, (C_3-C_7)cycloalkyl, -CN, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_1-C_6)alkyl-NH-. [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-. [(C_1-C_6)alkyl]$_2$-N-(C=O)-, (C_6-C_{10})aryl-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-S-, and (C_1-C_6)alkyl optionally substituted by one to four fluoro substituents.

[000173] 2-phenylpyran-4-one derivatives such as those described in U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula **XXXXXIII**:



XXXXXIII

wherein:

R^{256} represents an alkyl or –NR^{259} R^{260} group, wherein R^{259} and R^{260} each independently represents a hydrogen atom or an alkyl group;

R^{257} represents an alkyl, C_3 –C_7 cycloalkyl, naphthyl, tetrahydronaphthyl or

indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^{258} represents a methyl, hydroxymethyl, alkoxymethyl, C_3 –C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2 -- R^{261} group wherein R^{261} represents an alkyl group; and

X^{36} represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

[000174] Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:

3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,
3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,
2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-

one,

3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,

and pharmaceutically acceptable salts thereof.

[000175] Cox-2 selective inhibitors that are useful in the subject method and compositions can also include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); U.S. Patent Nos. 6,359,182 and 6,538,116 (C-nitroso compounds); U.S. Published Application No. 2003/0065011 (substituted pyridines); U.S. Published Application No. 2003/0207897 (substituted indole derivatives); and mixtures thereof.

[000176] Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

[000177] Preferred Cox-2 selective inhibitor compounds are those compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tabacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall

Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,0340256), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), prodrugs of any of them, and mixtures thereof.

[000178] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[000179] Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

[000180] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000181] Cox-2 inhibitors that are useful in the compositions and methods of present invention can also be synthesized, for example, according to the description in Example 1. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, in U.S. Patent No. 5,466,823 to Talley, *et al.*

[000182] By way of example, various classes of Cox-2 inhibitors useful in the present invention can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

[000183] Thiophene analogs useful in the present invention can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

[000184] Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

[000185] Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

[000186] Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

[000187] Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

[000188] Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

[000189] Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03,392.

[000190] Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

[000191] Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.

[000192] Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

[000193] Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

[000194] 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

[000195] Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

[000196] The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

[000197] The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

[000198] The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

[000199] The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

[000200] The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[000201] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

[000202] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

[000203] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[000204] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

[000205] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

[000206] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl-benzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

[000207] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[000208] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

[000209] An optional second component of the present invention is a weight-loss agent that is administered to a subject in combination with a Cox-2 inhibitor.

[000210] The present invention is directed to a novel method of treating or preventing obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more weight-loss agents.

[000211] As used herein, the term "weight-loss agent" refers to any chemical recognized as having an effect on a subject's weight over any duration of time other than a chemical that is an inhibitor of the Cox-2 enzyme. This effect can occur via appetite suppression, metabolic acceleration, adipogenesis inhibition, or any other mechanism. While not

to be construed as limiting, preferred examples of weight-loss agents are recited in Table 3 below.

[000212] Although, any combination of a Cox-2 inhibitor and weight-loss agent is encompassed by the present invention, preferred examples of weight-loss agents include those agents specifically recited in Table 3. Thus, it is further preferred that any weight-loss agent recited in Table 3 be combined in methods, compositions, pharmaceutical compositions, and kits with any Cox-2 inhibitor, and in preferred embodiments, any Cox-2 inhibitor that is described herein.

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A1	phentermine	Adipex, Fastin, Ionamin, Oby-trim	anorectic		15-30 mg daily	
A2	diethylpropion	Tenuate, Tenuate dospan, Tepanil	anorectic Catecholamine modulator	1-phenyl-2-diethyl-amino-1-propanone hydrochloride	25 mg three times daily	
A3	mazindol	Sanorex, Mazanor	anorectic Catecholamine modulator		1-3 mg daily	
A4	phendimetrazine	Adipost, Bontril, Plegine, Prelu-2, X-Trozine	anorectic		35 mg twice or three times daily	
A5	benzphetamine	Didrex	anorectic		25 to 50 mg one to three times daily	
A6	sibutramine	Meridia	norepinephrine,	cyclobutaneme	5 to 30 mg	

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			dopamine and serotonin reuptake inhibitor and Catecholamine modulator	thanamine 1-(4-chlorophenyl)-*N*, *N*-dimethyl-alfa-(2-methylpropyl)-, hydrochloride	daily	
A7	orlistat	Xenical	Lipase inhibitor	(S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester	120 mg three times daily	
A8	fenfluramine	Pondimin	anorectic	N-ethyl-alpha-methyl-3-(trifluoromethyl) benzeneethanamine hydrochloride	20 mg three times daily	

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A9	dexfenfluramine	Redux	dual serotonin reuptake inhibitor and serotonin releasing agent	(S)-N-ethyl-alpha-methyl-3-(trifluoromethyl) benzeneethanamine hydrochloride	15 to 30 mg daily	
A10	bupropion	Wellbutrin	aminoketone class antidepressant and is a serotonin reuptake inhibitor	(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride	150mg given twice daily	
A11	diazoxide	Proglycem	Activator of ATP-dependent K^+ channels	7-chloro-3-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide		
A12	Dehydro-epiandrosterone		metabolic accelerator			U.S. Patent No. 5,795,880 to Svec, *et al.*
A13	metformin	Glucophage	anti-hyperglycemic	N,N-dimethylimidodi		

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
				carbonimidic diamide hydrochloride		
A14	sertraline	Zoloft	serotonin reuptake inhibitor	(1S-cis)-4-(3,4-dichlorophenyl) -1,2,3,4-tetrahydro-N-methyl-1-nanphthalenamine hydrochloride		
A15	topiramate	Topamax	GABA enhancer and sodium channel blocker	2,3:4,5- bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate		
A16	(+) norfenfluramine		Serotonin and dopamine releaser			
A17	leptin derivatives and formulations					U.S Patent Nos. 5,552,524; 5,552,523; 5,552,522; 5,521,283

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A18			Histamine-3 antagonist			
A19	rimonabant		cannabinoid (CB1) receptor antagonist			
A20	aminorex		anorectic			
A21	adiponectin					
A22	phenylpropanolamine	Control, Dexatrim, Phenoxine	Alpha-adrenergic receptor agonists anorectic		25-100 mg daily	
A23	amantadine	Symmetrel	anorectic			
A24	nizatidine					
A25	cimetidine					
A26	amphetamine		B-phenethylamine			
A27	dinitrophenol					
A28	diethylpropion hydrochloride					
A29	mazindol benzphetamine					

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A30	phendimetrazine					
A31	phentermine		Catecholamine modulator			
A32	dexfenfluramine					
A33	amylin					
A34			melanocortin-4 receptor agonists			
A35			neuropeptide Y antagonists			WO 96/16542
A36			Beta(3)-adrenergic agonists			U.S. Pat. No. 5,541,677 and WO 95/29159
A37			glucagon-like peptide-1 agonists			
A38			PPAR-gamma antagonists and PPAR-gamma partial agonists			
A39			orexins			
A40			Dehydroepiandrosterone derivatives			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A41	mazindol					
A42	ephedrine	Ephedra				
A43	fenfluramine			N-ethyl-.alpha.-methyl-3(trifluoromethyl) benzeneethanamine hydrochloride	5 mg/kg daily	
A44			selective serotonin reuptake inhibitors			
A45			enterostatin agonist			
A46			galanin antagonist			
A47			urocortin agonist			
A48			CCK agonist			
A49			UCP activating agents			
A50	ergoset					
A51	fluoxetine hydrochloride	Prozac				

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A52	fluvoxamine maleate	Luvox				
A53	trazodone hydrochloride	Desyrel				
A54	Dehydro-epiandrosterone					
A55	glucocorticosteroid					
A56			Prolactin modulators			U.S. Patent No. 5,744,477 to Cincotta, *et al.*
A57	citalopram	Celexa				
A58			Growth-hormone secretagogues			U.S. Patent No. 6,110,932 to Carpino, *et al.*
A59			benzoazine derivative			U.S. Patent No. 5,710,152 to Nagao, *et al.*
A60	chromium picolinate		Chromium formulations and derivatives			
A61	L-glutamine					
A62	caffeine					
A63	methamphetamine	Desoxyn				

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
	hydrochloride					
A64	benzphetamine hydrochloride	Didrex				
A65	sumatriptan succinate	Imitrex				
A66				hydroxycitric acid		
A67			Ciliary neurotropic factor			
A68	human steroidal hormone (RF1051)					
A69	cholecystokinin					
A70	bombesin					
A71	glucagon					
A72	insulin					
A73	cyclohistidyl-proline					
A74	somatomedin					
A75			selective CRF agonist			
A76	apoprotein IV					

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A77			a1-adrenergic receptor agonists			
A78			antihistamine			
A79	digitalis					
A80	thyroid hormone					
			5-HT_{2C} agonists			WO-A-98/30548; EP-A-0655440; CA-2132887; and CA-2153937
A81			5-HT_{2A} agonist			
A82				(R)-N-›4-›2-››2-Hydroxy-2-(pyridin-3-yl)ethylaminoethyl-phenyl-4-›4-(3 -cyclopentylpropyl)-5-tetrazolon- 1-ylbenzenesulfonamide		WO 95/29159 and U.S. Pat. No. 5,561,142

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A83			Dopamine antagonist			
A84		Zymax				
A85		Ionamin				
A86	diazoxide	Proglycem				
A87	naltrexone	Revia				
A88	5-hydroxy tryptophan					
A89	hypericum					
A90			Adipocyte complement-related protein (Acrp30) and adipocyte complement-related protein (Acrp30) modulators			
A91			Adipsin modulators			
A92	botanical P57					
A93			Cannabinoid			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			antagonists			
A94			tyrosine phosphatase modulators			
A95	phytostanol					
A96			11beta hydroxysteroid dehydrogenase type 1 modulators			
A97	aminosterol					
A98	beacon					
A99	calpain 10					
A100	corticotropin releasing hormone					
A101			Cyclic AMP response element-binding protein modulators			
A102			Diacylglycerol o-acyltransferase			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			modulators			
A103			Fatty acid transport protein 4 modulators			
A104	follistatin					
A105	GATA					
A106			G protein beta-3 subunit 825T modulator			
A107			Ghrelin receptor antagonists			
A108			High mobility group 1C modulator			
A109			Kallikrein modulators			
A110			Melanin-concentrating hormone 'receptor modulators			
A111	oleylethanolamide					
A112			Perilipin			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			modulators			
			Tub gene modulators			
A113	Desmethyl-sibutramine					
A114	agouti protein					
A115			Anticonvulsants			
A116			Leptin receptor modulators			
A117	eltroxin					
A118	levothroid					
A119	tertroxin					
A120	synthroid					
A121	lonamin					
A122	phen-fen					
A123	eltroxin					
A124	cyronine					
A125	asenlix					
A126			Metabolic accelerators			
A127			Adipogenesis modulating			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			agents			
A128			Pyrroloquinolines			U.S. Patent No. 6,365,598 Adams , *et al.*
A129			NK-1 receptor antagonists			EP No. 0 577 394
A130	bisphenol A diglycidyl ether		PPAR-gamma antagonist			U. S. Patent No. 6,033,656 to Mikami, *et al.*
A131			PPAR-alpha agonists			U.S. Patent No. 6,028,109 to Willson
A132			Leptin agonists			

[000213] As described above, several weight-loss agents are available for the treatment or prevention of obesity, obesity-related complications and for causing weight-loss. The majority of available weight-loss agents are "anorectic(s)" or appetite-suppressant medications. Appetite-suppressant medications promote weight loss by decreasing appetite or increasing the feeling or sensation of being full. These medications decrease appetite by increasing levels of serotonin or catecholamine--two brain chemicals that affect mood and appetite. Preferred weight-loss agents include anorectic compounds that cause weight-loss through the suppression of a subject's appetite, which causes a reduction in the number of calories consumed.

[000214] Other preferred weight-loss agents effectuate weight-loss through molecular mechanisms via modulation of the process of adipogenesis (*i.e.* adipogenesis modulating agents). Slowing or halting adipogenesis will reduce the number and/or size of adipocytes or fat cells. Accordingly, the reduction in number or size of adipocytes will result in a subject's loss of weight.

[000215] As used herein, the term "adipogenesis modulating" means the interference at any point, or more than one point, within the natural (normally occurring) process of differentiation of a mesenchymal cell into a pre-adipocyte cell and then into a fully mature adipocyte. The terms "adipogenesis modulating" and "modulating adipogenesis", which may be used interchangeably herein, include either a decrease in the number of mature adipocytes or a decrease in the size of mature adipocytes. The term "adipogenesis modulating" also includes halting or suppressing further differentiation or development within the adipogenesis process. In some instances, modulating adipogenesis also includes increasing either the size or number of adipocytes. Thus, any departure from the natural process in the development of a mature adipocyte is encompassed by the term "adipogenesis modulating".

[000216] Examples of such agents capable of modulating adipogenesis include, but are not limited to, "PPAR-gamma antagonists", which modulate the process of adipogenesis by antagonism of the PPAR-gamma receptor itself or by down-regulation of PPAR-gamma receptor mRNA synthesis. As used herein, the term "mRNA" refers to messenger RNA. For example, U.S. Patent No. 6,033,656 to Mikami, *et al.* provides methods of suppressing the activation of PPAR-gamma in a mammalian body by administering to a subject in need of such therapy, an effective amount of the compound, bisphenol A diglycidyl ether.

[000217] Still other preferred weight-loss agents cause weight-loss by increasing the basal rate of metabolism in a subject (*i.e.* "metabolic accelerators"). These agents cause a subject to metabolically expend more calories than are ingested, thus, resulting in weight-loss. Metabolic accelerators have been used heretofore for drug therapies of obesity. For example, androgens such as dehydroepiandrosterone are known to have anti-obesity action (Japanese Patent Unexamined Publication No. (Hei)2-275895/1990). Such androgens are believed to activate intramuscular anabolism to induce the consumption of stored fat.

[000218] Therefore, in a preferred embodiment, the weight-loss agent is any compound capable of having any effect on a subject's weight through appetite suppression or by increasing the rate of metabolism, including compounds capable of modulating the process of adipogenesis *in vivo* or *in vitro*, but the weight-loss agent does not include compounds that are Cox-2 inhibitors.

[000219] More preferred is that the weight-loss agent comprises any of one or more agents selected from anorectics, serotonin reuptake inhibitors, serotonin releasing agents, activators of ATP-dependent K^+ channels, anti-hyperglycemics, amphetamines and amphetamine derivatives, melanocortin-4 receptor agonists, neuropeptide Y antagonists, lipase inhibitors, beta(3)-adrenergic agonists, glucagon-like peptide-1 agonists, PPAR-gamma antagonists, PPAR-gamma partial agonists, orexins, enterostatin agonists, galanin antagonists, urocortin agonists,

CCK agonists, UCP activating agents, prolactin modulators, growth-hormone secretagogues, benzoazine derivatives, ciliary neurotropic factor, selective CRF agonists, a1-adrenergic receptor agonists, antihistamines, 5-HT_{2C} agonists, 5-HT_{2A} agonists, catecholamine modulators, chromium formulations and derivatives, dopamine antagonists, adipocyte complement-related protein (Acrp30), adipocyte complement-related protein (Acrp30) modulators, adipsin modulators, cannabinoid antagonists, tyrosine phosphatase modulators, 11beta hydroxysteroid dehydrogenase type 1 modulators, cyclic AMP response element-binding protein modulators, diacylglycerol o-acyltransferase modulators, dehydroepiandrosterone derivatives, fatty acid transport protein 4 modulators, G protein beta-3 subunit 825T modulator, high mobility group 1C modulator, kallikrein modulators, melanin-concentrating hormone receptor modulators, perilipin modulators, tub gene modulators, alpha-adrenergic agonists, beta-adrenergic agonists, anticonvulsants, leptin receptor modulators, metabolic accelerators, adipogenesis modulating agents, pyrroloquinolines, NK-1 receptor antagonists, PPAR-alpha agonists, ghrelin receptor antagonists, leptin agonists, histamine-3 antagonists, and mixtures thereof.

[000220] Even more preferred is that the weight-loss agent comprises any one or more of the weight-loss treatment agents selected from group consisting of phentermine, diethylpropion, mazindol, phendimetrazine, benzphetamine, sibutramine, orlistat, fenfluramine, dexfenfluramine, bupropion, diazoxide, diethylpropion, metformin, sertraline, topiramate, (+)norfenfluramine, leptin derivatives and formulations, rimonabant, aminorex, adiponectin, phenylpropanolamine, amantadine, nizatidine, cimetidine, amphetamine, dinitrophenol, dehydroepiandrosterone, mazindol benzphetamine, phendimetrazine, phentermine, dexfenfluramine, amylin, mazindol, ephedrine, fenfluramine, ergoset, fluoxetine hydrochloride, fluvoxamine maleate, trazodone hydrochloride, dehydroepiandrosterone, glucocorticosteroid, citalopram, chromium picolinate, L-glutamine, caffeine, methamphetamine hydrochloride,

benzphetamine hydrochloride, sumatriptan succinate, human steroidal hormone (RF1051), cholecystokinin, bombesin, glucagon, insulin, cyclohistidyl-proline, somatomedin, apoprotein IV, digitalis, thyroid hormone, diazoxide, naltrexone, 5-hydroxy tryptophan, hypericum, botanical P57, phytostanol, aminosterol, beacon, calpain 10, corticotropin releasing hormone, follistatin, GATA, oleylethanolamide, agouti protein, eltroxin, levothroid, tertroxin, synthroid, lonamin, phen-fen, eltroxin, cyronine, asenlix, bisphenol A diglycidyl ether, desmethylsibutramine, and mixtures thereof.

[000221] More preferred still is that the weight-loss agent comprises any of one or more agents selected from the following classes of weight-loss treatment agents including anorectics, metabolic accelerators, lipase inhibitors, serotonin uptake inhibitors, adipocyte complement-related protein (Acrp30), adipocyte complement-related protein (Acrp30) modulators, serotonin release agents, catecholamine modulators, PPAR-gamma antagonists, PPAR-gamma partial agonists, and mixtures thereof.

[000222] More preferred is that the weight-loss agent is selected from the group consisting of anorectics, adipocyte complement-related protein (Acrp30) modulators, metabolic accelerators, PPAR-gamma antagonists, PPAR-gamma partial agonist classes of weight-loss agents, and mixtures thereof.

[000223] Even more preferred still is that the weight-loss agent comprises sibutramine or orlistat.

[000224] Any combination of the Cox-2 inhibitors and weight-loss agents that are described above can be used in the novel composition and the novel pharmaceutical composition. In one embodiment, one or more of an anorectic class of weight-loss agent is combined with at least one Cox-2 inhibitor. In another embodiment, one or more of an adipogenesis modulating agent (*e.g.*, PPAR gamma antagonists or partial agonists) is combined with at least one Cox-2 inhibitor. In still another embodiment, one or more metabolism modulating agents are combined with at least one Cox-2 inhibitor. Further encompassed by the present invention are any

combinations of anorectics, adipogenesis modulating agents, and metabolism modulating agents each independently, or any combinations thereof, are also combined with at least one Cox-2 inhibitor.

[000225] Thus, in a preferred embodiment, a Cox-2 inhibitor such as, for example, celecoxib can be combined with any combination of anorectics, adipogenesis modulating agents, or metabolism modulating agents, each independently or any combinations thereof. For example, a Cox-2 inhibitor such as, celecoxib, can be combined with any of the aforementioned weight-loss agents cited in Table 3, such as sibutramine.

[000226] In a preferred embodiment, the present invention encompasses a therapeutic composition comprising a Cox-2 inhibitor and a weight-loss agent.

[000227] Cox-2 inhibitors and weight-loss agents that are useful in the present invention can be of any purity or grade, as long as the preparation is of a quality suitable for pharmaceutical use. The Cox-2 inhibitors and weight-loss agents can be provided in pure form, or it can be accompanied with impurities or commonly associated compounds that do not affect its physiological activity or safety. The Cox-2 inhibitors and weight-loss agents can also be supplied in the form of a prodrug, an isomer, a tautomer, a racemic mixture, or in any other chemical form or combination that, under physiological conditions, still provides for inhibition of the Cox-2 enzyme.

[000228] The compositions of the present invention can comprise a Cox-2 inhibitor and a weight-loss agent as an active ingredient or a pharmaceutically acceptable salt, thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

[000229] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic,

fumaric, pyruvic, aspartic, glutamic, benzoic, hydrochloric, trifluoroacetic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[000230] Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts.

[000231] Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[000232] Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences.

[000233] Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N, N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and

procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[000234] All of the above salts and ions can be prepared by those skilled in the art by conventional means from the corresponding compounds of the present invention.

[000235] In the present invention, a Cox-2 inhibitor and/or weight-loss agent are administered to a patient in need of such treatment or prevention according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor and the weight-loss agent depend upon the needs of the subject being treated, the type of treatment or prevention, the efficacy of the compound and the degree of disease severity in the subject.

[000236] The combination of a Cox-2 inhibitor and a weight-loss agent can be provided in a pharmaceutically acceptable carrier or excipient to form a pharmaceutical composition. In a preferred embodiment, the present invention encompasses a pharmaceutical composition comprising a Cox-2 inhibitor, a weight-loss agent, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product.

[000237] The compositions of the present invention may be administered enterally and/or parenterally. Oral (intra-gastric) is a preferred route of administration. Pharmaceutically acceptable carriers can be in solid dosage forms for the methods of the present invention, which include tablets, capsules, pills, and granules, which can be prepared with coatings and shells, such as enteric coatings and others well known in the art. Liquid dosage forms for oral administration include

pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs.

[000238] Enteral administration includes solution, tablets, sustained release capsules, enteric-coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[000239] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[000240] Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, maize starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[000241] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000242] Aqueous suspensions can be produced that contain the active materials in a mixture with excipients suitable for the manufacture of

aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000243] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000244] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000245] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[000246] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000247] Syrups and elixirs containing the Cox-2 inhibitor and/or weight-loss agent may be formulated with sweetening agents, for example glycerol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[000248] The subject method of prescribing a Cox-2 inhibitor and/or weight-loss agent and compositions comprising the same can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art.

[000249] Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents, which have been mentioned above or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[000250] Administration of either one or both of the Cox-2 inhibitor and weight-loss agents can also be by inhalation, in the form of aerosols or solutions for nebulizers. Therefore, in one embodiment, the Cox-2 inhibitor and/or the weight-loss agent is administered by direct inhalation into the respiratory system of a subject for delivery as a mist or other aerosol or dry powder. Delivery of drugs or other active ingredients directly to the subject's lungs provides numerous advantages including, providing an extensive surface area for drug absorption, direct delivery of

therapeutic agents to the disease site in the case of regional drug therapy, eliminating the possibility of drug degradation in the subject's intestinal tract (a risk associated with oral administration), and eliminating the need for repeated subcutaneous injections.

[000251] Aerosols of liquid particles comprising the active materials may be produced by any suitable means, such as inhalatory delivery systems. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier. The carrier is typically water, and most preferably sterile, pyrogen-free water, or a dilute aqueous alcoholic solution, preferably made isotonic, but may be hypertonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, as well as antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, which are normally used in the preparation of pharmaceutical compositions.

[000252] Aerosols of solid particles comprising the active materials may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration.

[000253] One type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder

delivered by means of air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active materials, a suitable powder diluent, such as lactose, and an optional surfactant.

[000254] A second type of aerosol generator is a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the Cox-2 inhibitor and/or the weight-loss agent in a liquified propellant. During use, the metered dose inhaler discharges the formulation through a valve, adapted to deliver a metered volume, to produce a fine particle spray containing the active materials. Any propellant may be used for aerosol delivery, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants.

[000255] A third type of aerosol generator is a electrohydrodynamic (EHD) aerosol generating device, which has the advantage of being adjustable to create substantially monomodal aerosols having particles more uniform in size than aerosols generated by other devices or methods. Typical EHD devices include a spray nozzle in fluid communication with a source of liquid to be aerosolized, at least one discharge electrode, a first voltage source for maintaining the spray nozzle at a negative (or positive) potential relative to the potential of the discharge electrode, and a second voltage source for maintaining the discharge electrode at a positive (or negative) potential relative to the potential of the spray nozzle.

[000256] Most EHD devices create aerosols by causing a liquid to form droplets that enter a region of high electric field strength. The electric field then imparts a net electric charge to these droplets, and this net electric charge tends to remain on the surface of the droplet. The repelling force of the charge on the surface of the droplet balances against the surface tension of the liquid in the droplet, thereby causing the droplet to form a cone-like structure known as a Taylor Cone. In the tip of this cone-like

structure, the electric force exerted on the surface of the droplet overcomes the surface tension of the liquid, thereby generating a stream of liquid that disperses into a many smaller droplets of roughly the same size. These smaller droplets form a mist which constitutes the aerosol cloud that the user ultimately inhales.

[000257] In a preferred embodiment, the administration of the compositions of the present invention can also be by a rectal route of delivery. Rectal routes of delivery are in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient, which is solid at ordinary temperature, but liquid at the rectal temperature and will therefore, melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[000258] Also encompassed by the present invention is buccal or "sub-lingual" administration, which includes lozenges or a chewable gum comprising the compounds, set forth herein. The compounds can be deposited in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compounds in an inert base such as gelatin and glycerin or sucrose and acacia.

[000259] The prevent invention further encompasses intranasal administration comprising the compounds set forth herein. Intranasal dosage forms include, but are not limited to, aerosols, drops, gels, powders, and mixtures thereof.

[000260] Other methods for administration of the Cox-2 inhibitor compound and/or the weight-loss agent include dermal patches that release the medicaments directly into a subject's skin.

[000261] Topical delivery systems are also encompassed by the present invention and include ointments, powders, sprays, creams, jellies, collyriums, solutions or suspensions.

[000262] The compositions of the present invention can optionally be supplemented with additional agents such as, for example, viscosity enhancers, preservatives, surfactants and penetration enhancers.

[000263] Viscosity is an important attribute of many medications. Drops that have a high viscosity tend to stay in the body for longer periods and thus, increase absorption of the active compounds by the target tissues or increase the retention time. Such viscosity-building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

[000264] Preservatives are optionally employed to prevent microbial contamination during use. Suitable preservatives include polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically, such preservatives are employed at a level of from 0.001% to 1.0% by weight.

[000265] The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (*e.g.* Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically, such co-solvents are employed at a level of from 0.01% to 2% by weight.

[000266] A penetration enhancer is an agent used to increase the permeability of the skin to an active agent to increase the rate at which the drug diffuses through the skin and enters the tissues and bloodstream. Thus, in one embodiment of the present invention, a penetration enhancer may be added to a Cox-2 inhibitor topical composition or a Cox-2 inhibitor and weight-loss agent topical composition.

[000267] Examples of penetration enhancers suitable for use with the compositions of the present invention include: alcohols, such as ethanol and isopropanol; polyols, such as n-alkanols, limonene, terpenes,

dioxolane, propylene glycol, ethylene glycol, other glycols, and glycerol; sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide; esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl proprionate, and capric/caprylic triglycerides; ketones; amides, such as acetamides; oleates, such as triolein; various surfactants, such as sodium lauryl sulfate; various alkanoic acids, such as caprylic acid; lactam compounds, such as azone; alkanols, such as oleyl alcohol; dialkylamino acetates, and admixtures thereof.

[000268] Pharmaceutically acceptable excipients and carriers encompass all the foregoing and the like. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks. *See e.g.* Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 20th Edition, (Lippincott, Williams and Wilkins), 2000; Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, *et al.*, Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, *et al.*, Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

[000269] In other preferred embodiments, the present invention encompasses a kit for preventing or treating obesity or an obesity-related complication in a subject that is in need of such prevention or treatment, the kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a weight-loss agent.

[000270] It will be appreciated that the amount of the Cox-2 inhibitor and the weight-loss agent required for use in the treatment or prevention of obesity and obesity-related complications will vary depending upon the particular compounds or compositions selected.

[000271] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage is described herein,

although the limits that are identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages. Various delivery systems include capsules, tablets, food, chewing gum, lozenges, dermal patches, and gelatin capsules, for example.

[000272] The appropriate dosage level of a Cox-2 inhibitor will generally be from about 0.01 mg per kg to about 140 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 mg/kg to about 25 mg/kg per day; more preferably about 0.5 mg to about 10 mg/kg per day.

[000273] In larger mammals, for example humans, a typical indicated dose is about 0.5 mg to 7 grams orally per day. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

[000274] The amount of the Cox-2 inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 7 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms for the Cox-2 inhibitor will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

[000275] The dosage level of a weight-loss agent will necessarily depend on the particular agent that is used. However, in general, the appropriate dosage level of a weight-loss agent will generally be from about 0.002 mg per kg to about 10 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 mg/kg to about 7 mg/kg per day; more preferably about 0.1 mg to about 5 mg/kg per day.

[000276] The exact dosage and regimen for administering a Cox-2 inhibitor alone or in combination with a weight-loss agent will necessarily depend upon the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances. Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[000277] To determine the effectiveness of a particular dosage of a Cox-2 inhibitor alone or in combination with a weight-loss agent, desirable weight standards are derived by comparing a particular subject's weight to a mathematical formula known as Body Mass Index (BMI), which represents weight levels associated with the lowest overall risk to health. *See e.g.* Garrow JS and Webster J. Quetelet's index (W/H^2) as a measure of fatness, *International Journal of Obesity 9*:147-153 (1985); Gallagher D, *et al.* How useful is BMI for comparison of body fatness across age, sex and ethnic groups? *American Journal of Epidemiology 143*:228-239 (1996); Willett W, et al. Guidelines for healthy weight. *New England Journal of Medicine 341*:427-434 (1999); World Health Organization. Physical status: The use and interpretation of anthropometry. Geneva, Switzerland: World Health Organization. *WHO Technical Report* Series (1995); Calle EE, *et al.* BMI and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine 341*:1097-1105 (1999).

[000278] Where BMI is utilized as a measure of weight, an individual is considered overweight when BMI values range between 25.0 and 29.9. Obesity is defined for BMI values of greater than or equal to 30.0. For example, the World Health Organization assigns BMI values as follows: 25.0-29.9, Grade I obesity (moderately overweight); 30-39.9, Grade II obesity (severely overweight); and 40.0 or greater, Grade III obesity (massive/morbid obesity). Using weight tables, obesity is classified as mild (20-40% overweight), moderate (41-100% overweight), and severe

(>100%) overweight. Thus, individuals 20% over ideal weight guidelines are considered obese. Individuals 1-19.9% over ideal weight are classified as overweight.

[000279] Another way to determine the effectiveness of a particular dosage of a Cox-2 inhibitor alone or in combination with a weight-loss agent is to observe or measure its effect upon the process of adipogenesis or upon an adipogenesis-related disorder. This may be achieved by any of the techniques known to those practiced in the art of measuring lean vs. fat body mass composition.

[000280] The term "adipogenesis" refers, in a general sense to the process by which undifferentiated precursor cells differentiate into fat cells. Specifically, adipogenesis is a physiological developmental process by which an undifferentiated mesenchymal cell differentiates into a pre-adipocyte cell, which then undergoes a secondary differentiation step to become a lipid-filled mature adipocyte. Thus, the term adipogenesis is meant to encompass the entire developmental process from undifferentiated mesenchymal cell to a fully developed and mature adipocyte cell. As used herein, the terms "adipogenesis-related disorder" refers to any physiological condition in a subject wherein the normal process of adipogenesis has been altered. For example, where the process of adipogenesis occurs too frequently or too excessively, it can result in the physiological condition of obesity.

[000281] Several protocols have been reported for observing and measuring the effect of a given compound or treatment or therapy upon adipogenesis or pre-adipocyte differentiation. *See e.g.* Abbott, D., *et al., J. Biol. Chem. 272(51)*:32454-32462 (1997); Gregoire, F., *et al., Physiolog. Reviews 78(3)*:783-809 (1998); Kelly, K., *et al., Endocrinology 139(5)*:2622-2628 (1998); Fowler, S., *et al., J. Histochem. Cytochem. 8*:833-836 (1985); and Greenspan, P., *et al., J. Cell. Biol. 100*:965-972 (1985).

[000282] As used herein, the term "subject" for purposes of treatment includes any subject, and preferably is a subject who is in need of the

prevention and/or treatment of obesity, or who has weight-related disorder or a weight-related or obesity complication. The subject is typically an animal, and yet more typically is a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc. Preferably, the mammal is a human. For methods of prevention, the subject is any subject, and preferably is a subject that is in need of prevention and/or treatment of obesity or a weight-related disorder or an obesity-related complication. Veterinary use for weight reduction of domestic animals or food production uses of this therapy to improve fat/muscle ratios and thus, food taste and quality are also encompassed by the present invention.

[000283] As used herein, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" refer to any subject who is suffering from or is predisposed to obesity or any obesity-related complication described herein. Also, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" refer to any subject who desires to lose weight and is not necessarily suffering from obesity or being overweight or suffering from a obesity-related disorder. Thus, any subject who desires to lose any amount of weight is encompassed by the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication".

[000284] The terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" also refer to any subject that requires a lower dose of weight-loss agents. In addition, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" means any subject who requires a reduction in the side-effects of a weight-loss agent. Furthermore, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" means any subject who requires improved tolerability to any weight-loss agent for obesity therapy. Finally, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related

complication" means any subject who requires or desires the physiological modulation of the process of adipogenesis.

[000285] The present invention also encompasses the therapeutic treatment and prevention of several obesity-related complications. According to the NIH Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, all adults (aged 18 years or older) who have a BMI of 25 or more are considered at risk for premature death and disability as a consequence of overweight and obesity. These health risks increase even more as the severity of a subject's obesity increases.

[000286] Therefore, the present invention encompasses the treament and prevention of situations where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of high blood pressure, hypertension, high blood cholesterol, dyslipidemia, type 2 diabetes, Insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, cardiovascular disease, angina pectoris, congestive heart failure, stroke, gallstones, cholescystitis, cholelithiasis, gout, osteoarthritis, rheumatoid arthritis, obstructive sleep apnea, respiratory problems, cancer (such as endometrial, breast, prostate and colon cancers), complications of pregnancy, poor female reproductive health irregularities (such as menstrual irregularities, infertility and irregular ovulation), bladder control problems (such as stress incontinence), uric acid nephrolithiasis, psychological disorders (such as depression, eating disorders, distorted body image and low self esteem), coronary heart disease, atherosclerotic diseases, artherosclerosis, stable angina, unstable angina, type II diabetes, sleep apnea; high LDL cholesterol, low HDL cholesterol, high triglycerides, high blood glucose and including any other disorders or complications that are amenable to amelioration through inhibition of the Cox-2 enzyme alone or in combination with administration to a subject in need of such treatment of an effective amount of the weight-loss agents referred to herein.

[000287] More preferred is where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of rheumatoid arthritis, artherosclerosis, stable angina, unstable angina, hypertension, dyslipidemia, type 2 diabetes, stroke, gallbladder disease, cardiovascular disease, osteoarthritis, hypercholesterolemia, sleep apnea, respiratory problems, cancer and stroke.

[000288] Even more preferred is where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of cardiovascular disease, osteoarthritis, rheumatoid arthritis, artherosclerosis, stable angina, unstable angina, hypertension and hypercholesteremia.

[000289] Still further preferred is where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of cardiovascular disease, osteoarthritis, rheumatoid arthritis, artherosclerosis, stable angina and unstable angina.

[000290] Preferably, the present invention also encompasses the treatment and prevention of obesity and obesity-related complications and provides methods and compositions for causing weight-loss in a subject that desires to lose weight.

[000291] The methods and compositions of the present invention not only encompass the prevention or treatment of obesity and obesity-related disorders in humans, but also in several animals. For example, many animals also suffer adverse consequences related to obesity. Obese cats and dogs have a greater risk for diseases including osteoarthritis, ligament injuries, perineal dermatitis, diabetes mellitus, cardiomyopathy, and urologic syndrome. Therefore, the methods and compositions of the present invention are useful to maintain a healthy weight in family pets in order to minimize disease risk. *See* U.S. Patent No. 6,071,544 to Sunvold.

[000292] Accordingly, besides being useful for humans, the methods and compositions of the present invention also encompass the treatment

and prevention of obesity and obesity-related disorders in other mammals, including horses, dogs, cats, rats, mice, sheep, pigs, cattle, hamsters, gerbils, and the like.

[000293] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

EXAMPLE 1

[000294] This example illustrates the preparation of the Cox-2 inhibitor, celecoxib.

[000295] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[000296] Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[000297] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

[000298] To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture

was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of C_{17} H_{14} N_3 O_2 SF_3 ; C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

[000299] This illustrates the production of a composition containing the Cox-2 inhibitor, celecoxib and the weight-loss agent, sibutramine, and of a pharmaceutical composition containing the combination.

[000300] Sibutramine may be synthesized by following the procedures of U.S. Patent Nos. 4,746,680; 4,929,629; or 5,436,272 or it may be supplied by any one of several commercially available preparations. One such preparation can be obtained under the trade name Meridia® from Abbott Laboratories, North Chicago, IL.

[000301] Each caplet of Meridia® contains 10 mg of sibutramine.

[000302] Celecoxib can be prepared as described in Example 1, or it can be obtained under the trade name Celebrex® from Pharmacia Corporation, Peapack, NJ.

[000303] A therapeutic composition of the present invention can be formed by intermixing sibutramine, 10 g; and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Example 1, or as available from Pharmacia Corporation, Peapack, NJ, under the tradename Celebrex®), in a suspension or solution with a sterile pharmaceutically acceptable liquid.

[000304] After mixing, the combination of sibutramine and celecoxib forms a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 10 mg of loperamide HCl and about 200 mg of celecoxib.

[000305] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed

into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains can contain about the same amount of the active ingredients as each of the single dose units of the liquid preparation described above.

[000306] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000307] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000308] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.